National Comprehensive Cancer Network®

NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®)

# Acute Myeloid Leukemia

Version 3.2023 — April 5, 2023

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National Comprehensive Cancer Network®

# NCCN Guidelines Version 3.2023
# Acute Myeloid Leukemia (Age ≥18 years)

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***Daniel A. Pollyea, MD, MS/Chair ‡ Þ †**
University of Colorado Cancer Center

**Jessica K. Altman, MD/Vice Chair ‡**
Robert H. Lurie Comprehensive Cancer Center of Northwestern University

**Dale Bixby, MD, PhD ‡ † Þ**
University of Michigan Rogel Cancer Center

**Amir T. Fathi, MD ‡ † Þ**
Massachusetts General Hospital Cancer Center

**James M. Foran, MD †**
Mayo Clinic Comprehensive Cancer Center

**Ivana Gojo, MD ‡**
The Sidney Kimmel Comprehensive Cancer Center at Johns Hopkins

**Aric C. Hall, MD ‡ † ξ**
University of Wisconsin Carbone Cancer Center

**Brian A. Jonas, MD, PhD ‡**
UC Davis Comprehensive Cancer Center

**Ashwin Kishtagari, MD ‡**
Vanderbilt-Ingram Cancer Center

**Jeffrey Lancet, MD ‡ †**
Moffitt Cancer Center

**Lori Maness, MD ‡**
Fred & Pamela Buffett Cancer Center

**James Mangan, MD, PhD ‡ ξ**
UC San Diego Moores Cancer Center

**Gabriel Mannis, MD ‡ Þ**
Stanford Cancer Institute

**Guido Marcucci, MD † Þ**
City of Hope National Medical Center

**Alice Mims, MD, MS †**
The Ohio State University Comprehensive Cancer Center - James Cancer Hospital and Solove Research Institute

**Kelsey Moriarty, MS, CGC**
UT Southwestern Simmons Comprehensive Cancer Center

**Moaath Mustafa Ali, MD, MPH ‡**
Case Comprehensive Cancer Center/ University Hospitals Seidman Cancer Center and Cleveland Clinic Taussig Cancer Institute

**Jadee Neff, MD, PhD ≠**
Duke Cancer Institute

**Reza Nejati, MD ≠**
Fox Chase Cancer Center

**Rebecca Olin, MD, MS ‡ ξ**
UCSF Helen Diller Family Comprehensive Cancer Center

**Mary-Elizabeth Percival, MD, MS ‡**
Fred Hutchinson Cancer Center

**Alexander Perl, MD †**
Abramson Cancer Center at the University of Pennsylvania

**Amanda Przespolewski, DO ‡**
Roswell Park Comprehensive Cancer Center

**Dinesh Rao, MD, PhD ≠**
UCLA Jonsson Comprehensive Cancer Center

**Farhad Ravandi, MD Þ ‡**
The University of Texas MD Anderson Cancer Center

**Rory Shallis, MD ‡**
Yale Cancer Center/Smilow Cancer Hospital

**Paul J. Shami, MD ‡**
Huntsman Cancer Institute at the University of Utah

**Eytan Stein, MD ‡**
Memorial Sloan Kettering Cancer Center

**Richard M. Stone, MD ‡ †**
Dana-Farber/Brigham and Women's Cancer Center

**Stephen A. Strickland, MD, MSCI ‡**
Vanderbilt-Ingram Cancer Center

**Kendra Sweet, MD, MS ‡ Þ †**
Moffitt Cancer Center

**Swapna Thota, MD ‡**
St. Jude Children's Research Hospital/The University of Tennessee Health Science Center

**Geoffrey Uy, MD † ‡ ξ**
Siteman Cancer Center at Barnes-Jewish Hospital and Washington University School of Medicine

**Pankit Vachhani, MD ‡**
O'Neil Comprehensive Cancer Center at UAB

**NCCN**
**Carly J. Cassara, MSc**
**Deborah Freedman-Cass, PhD**
**Katie Stehman, PA-C, MMS**

[NCCN Guidelines Panel Disclosures]

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ξ Bone marrow transplantation
‡ Hematology/Hematology oncology
Þ Internal medicine
† Medical oncology
≠ Pathology
* Discussion Section Writing Committee Member

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**Clinical Trials:** NCCN believes that the best management for any patient with cancer is in a clinical trial. Participation in clinical trials is especially encouraged.

Find an NCCN Member Institution: https://www.nccn.org/home/member-institutions.

**NCCN Categories of Evidence and Consensus:** All recommendations are category 2A unless otherwise indicated.

See NCCN Categories of Evidence and Consensus.

**NCCN Categories of Preference:** All recommendations are considered appropriate.

See NCCN Categories of Preference.

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**Updates in Version 3.2023 of the NCCN Guidelines for Acute Myeloid Leukemia from Version 2.2023 include:**

**MS-1**

- **The BPDCN section of the discussion has been updated.**

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**Updates in Version 2.2023 of the NCCN Guidelines for Acute Myeloid Leukemia from Version 1.2023 include:**

**AML-3**

- **Erratum: Re-induction for significant residual disease without a hypocellular BM, regimen added back after inadvertent removal: 7+3 (mitoxantrone) (for age ≥60 y)**
- **Erratum: Re-induction for significant cytoreduction, regimen added back after inadvertent removal: 7+3 (mitoxantrone) (for age ≥60 y)**

**AML-E 1 of 9**

- **Erratum: FLAG-IDA + venetoclax regimen: HiDAC dosing modified from 2 g/m$^2$ to 1.5 g/m$^2$**

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**Updates in Version 1.2023 of the NCCN Guidelines for Acute Myeloid Leukemia from Version 3.2022 include:**

**Global**

- **Terminologies modified to be more inclusive, including of all sexual orientations and gender identities.**

**EVAL-1**

- **Evaluation, bullet 5 modified: Bone marrow (BM) core biopsy and aspirate analyses, including immunophenotyping by immunohistochemistry (IHC) stains + flow cytometry, and ~~cytogenetic analyses (karyotype + FISH)~~ the analysis of chromosomal structural variations by cytogenetics, fluorescence in situ hybridization (FISH), or whole genome sequencing (See AML-A)**

**EVAL-1A**

- **Footnote a modified: A variety of gene mutations are associated with specific prognoses (category 2A) and may guide medical decision-making (category 2B). Other genetic lesions may have therapeutic significance. The field of genomics in myeloid malignancies and related implications in AML are evolving rapidly. Mutations should be tested in all patients. Multiplex gene panels and ~~comprehensive~~ targeted next-generation sequencing (NGS) analysis are recommended for the ongoing management of AML and various phases of treatment. (Papaemmanuil E, et al. N Engl J Med 2016;374:2209-2221; Lindsley RC, et al. Blood 2015;125:1367-1376; Dohner H, et al. Blood 2017;129:424-447) (see Discussion). If a test is not available at your institution, consult the pathology team (prior to performing the BM evaluation) about preserving material from the original diagnostic sample for future testing at an outside reference lab. Peripheral blood may alternatively be used to detect molecular abnormalities in patients with disease with morphologically detectable, circulating leukemic blasts.**
- **Footnote removed: The WHO 2016 classification defines acute leukemia as ≥20% blasts in the marrow or blood. In an appropriate clinical setting, a diagnosis of AML may be made with less than 20% in patients with the following cytogenetic abnormalities: t(15;17), t(8;21), t(16;16), inv(16). AML evolving from MDS (AML-MDS) is often more resistant to cytotoxic chemotherapy than AML that arises without antecedent hematologic disorder and may have a more indolent course. Some clinical trials designed for highgrade MDS may allow enrollment of patients with AML-MDS.**
- **Footnotes added:**
  - **d: Khoury JD, et al. Leukemia 2022;36:1703-1719.**
  - **j:Arber DA, et al. Blood 2022;140:1200-1228.**
  - **i: Kim K, et al. Am J Hematol. 2022;97:885-894.**

**Acute Promyelocytic Leukemia**

**APL-1**

- **Footnote a modified: Therapy-related APL is treated the same as de novo APL. FLT3 inhibitors are not recommended for FLT3-positive APL. Gale RE, et al. Blood 2005;106:3768-3776.**

Continued

**UPDATES**

**Updates in Version 1.2023 of the NCCN Guidelines for Acute Myeloid Leukemia from Version 3.2022 include:**

**APL-2**

- **APL Treatment Induction (Low-Risk), Preferred Regimens**
  - **Pathway 1 and Pathway 2, bullet 1 modified: If blood count recovery by day 28 (platelet >100,000, absolute neutrophil count (ANC) >1,000), proceed with consolidation. BM aspirate and biopsy may be considered to document <5% blasts and no abnormal promyelocytes ~~morphologic remission~~ but is optional**
  - **Pathway 1 and Pathway 2, bullet 2 modified: If full course of induction treatment not given, or counts have not recovered by day 28–35, a BM aspirate and biopsy is recommended to document <5% blasts and no abnormal promyelocytes ~~morphologic remission~~ before proceeding with consolidation but is optional**
- **APL Treatment Induction (Low-Risk), Useful in Certain Circumstances**
  - **Regimen 1 modified: ATRA 45 mg/m$^2$ in 2 divided doses daily + idarubicin 12 mg/ m$^2$ on days 2, 4, 6, 8 or on days 2, 4, 6 for aged >70 y (category 1)**
  - **Pathway 2 modified: BM aspirate and biopsy days 28–35 to document ~~morphologic remission~~ <5% blasts and no abnormal promyelocytes before proceeding with consolidation**

**APL-2A**

- **Footnote g modified: QTc and monitoring and optimizing electrolytes are important in safe administration of arsenic trioxide. See Arsenic trioxide monitoring in Principles of Supportive Care for APL (APL-A). Electrocardiogram (ECG) is recommended prior to initiating arsenic trioxide. During therapy, if a patient presents with a prolonged QT interval, the use of QTcF correction formula is recommended. Interventions such as minimizing concurrent QT-prolonging drugs and electrolyte correction are recommended prior to discontinuing arsenic trioxide.**
- **Footnote h modified: Lo-Coco F, et al. N Engl J Med 2013;369:111-121. Begin prophylaxis with prednisone; the optimal duration of steroid prophylaxis is unknown. ~~through completion of induction.~~ If differentiation syndrome develops, change to dexamethasone. See Principles of Supportive Care for APL (APL-A).**
- **Footnote l modified: If no evidence of morphologic disease ~~(ie, absence of blasts and abnormal promyelocytes)~~ (<5% blasts and no abnormal promyelocytes), discontinue ATRA and arsenic trioxide to allow for peripheral blood recovery since arsenic trioxide can be associated with significant myelosuppression. If evidence of morphologic disease, continue ATRA and arsenic trioxide and repeat BM 1 week later**
- **Footnote added: If full course of induction not given, BM biopsy should still be performed.**

**APL-3**

- **APL Treatment Induction (High-Risk), Other Recommended Regimens, regimen 3 modified: ATRA 45 mg/m$^2$ in 2 divided doses daily + idarubicin 12 mg/m$^2$ on days 2, 4, 6, 8 or on days 2, 4, 6 for those aged >70 y**
- **Consolidation Therapy**
  - **Pathway 2 modified: Arsenic trioxide 0.15 mg/kg daily 5 d/wk for 4 weeks every 8 weeks for a total of 4 cycles + ATRA 45 mg/m$^2$ for 2 weeks every 4 weeks for a total of 7 cycles. If ATRA or arsenic trioxide discontinued due to toxicity, a single dose of gemtuzumab ozogamicin 9 mg/m$^2$ may be given ~~once~~ every ~~4–5 weeks until 28 weeks from CR~~ 4–5 weeks provided platelets and ANC recover to ≥100 and ≥1.0, respectively, until molecular complete response (CR)**
  - **Pathway 3 modified: ATRA 45 mg/m$^2$ for 2 weeks every 4 weeks (or for 2 weeks on 2 weeks off) in consolidation courses 1–4 + arsenic trioxide 0.3 mg/kg on days 1–5 of week 1 in consolidation courses 1–4 and 0.25 mg/kg twice weekly in weeks 2–4 in consolidation courses 1–4 (category 1). If ATRA or arsenic trioxide discontinued due to toxicity, a single dose of gemtuzumab ozogamicin 9 mg/m$^2$ may be given ~~once~~ every ~~4–5 weeks until 28 weeks from CR~~ 4–5 weeks provided platelets and ANC recover to ≥100 and ≥1.0, respectively, until molecular CR**
  - **Pathway 5 modified: Daunorubicin 60 mg/m$^2$ x 3 days + cytarabine 200 mg/m$^2$ x 7 days x 1 cycle, then cytarabine 2 g/m$^2$ (aged <50 y) or 1.5 g/m$^2$ (aged 50–60 y) every 12 h x 5 days or 1 g/m$^2$ (aged >60 y) every 12 h x 4 days + daunorubicin 45 mg/m$^2$ x 3 days x 1 cycle + 5 doses of IT chemotherapy**

Continued

UPDATES

**Updates in Version 1.2023 of the NCCN Guidelines for Acute Myeloid Leukemia from Version 3.2022 include:**

**APL-3A**

- Footnote g modified by adding: ECG is recommended prior to initiating arsenic trioxide. During therapy, if a patient presents with a prolonged QT interval, the use of QTcF correction formula is recommended. Interventions such as minimizing concurrent QT-prolonging drugs and electrolyte correction are recommended prior to discontinuing arsenic trioxide.
- Footnote k added: Estey E, et al. Blood 2002;99:4222-4224.
- Footnote q modified by removing: It is important for regimens containing ATRA and arsenic trioxide to be administered for the management of APL. If arsenic is not available or contraindicated, it may be omitted from induction.
- Footnote z modified: Dose adjustment of cytarabine may be needed for ~~older~~ patients >60 years or patients with renal dysfunction
- Footnote aa added: High-risk patients who are >60 years did not receive cytarabine in consolidation and were treated as intermediate-risk patients in the LPA2005 study.
- Footnote bb added: Mitoxantrone was reduced to 3 days in intermediate-risk patients in the LPA2005 study.

**APL-4**

- Induction Therapy: Prolonged QTc, third regimen modified: ATRA 45 mg/m$^2$ in 2 divided doses daily + idarubicin 12 mg/m$^2$ on days 2, 4, 6, 8 or on days 2, 4, 6 for those aged >70 y
- Consolidation Therapy: Low EF
  - Sentence 2 in pathways 1 and 2 modified: If ATRA or arsenic trioxide discontinued due to toxicity, a single dose of gemtuzumab ozogamicin 9 mg/m$^2$ may be given ~~once~~ every ~~4–5 weeks until 28 weeks from CR~~ 4–5 weeks provided platelets and ANC recover to ≥100 and ≥1.0, respectively, until molecular CR
- Consolidation Therapy: Prolonged QTc
  - Pathway 1 modified: ATRA 45 mg/m$^2$ in 2 divided doses daily during weeks 1–2, 5–6, 9–10, 13–14, 17–18, 21–22, and 25–26. ~~A single dose of g~~Gemtuzumab ozogamicin 9 mg/m$^2$ may be given monthly until ~~achievement of complete~~ molecular ~~response~~CR
  - Pathway 2 modified: Daunorubicin 60 mg/m$^2$ x 3 days + cytarabine 200 mg/m2 x 7 days x 1 cycle, then cytarabine 2 g/m$^2$ (aged <50 y) or 1.5 g/m$^2$ (age 50–60 y) every 12 h x 5 days or 1 g/m$^2$ (aged >60 y) every 12 h x 4 days, + daunorubicin 45 mg/m$^2$ x 3 days x 1 cycle + 5 doses of IT chemotherapy

**APL-6**

- Therapy for relapse, Early relapse (<6 mo) after ATRA and arsenic trioxide (no anthracycline) pathway modified: Anthracycline-based regimen as per APL-3 or gemtuzumab ozogamicin
- Footnote kk added: See NCCN Guidelines for Hematopoietic Cell Transplantation.

**APL-A**

- APL differentiation syndrome, sub-bullet 1 modified: ~~If steroids are not initiated at time of treatment with ATRA and arsenic,~~ Maintain a high index of suspicion of APL differentiation syndrome (ie, fever, often associated with increasing WBC count >10,000/mcL, usually at initial diagnosis or relapse; shortness of breath; hypoxemia; pleural or pericardial effusions).3 Close monitoring of volume overload and pulmonary status is indicated. Initiate dexamethasone at first signs or symptoms of respiratorycompromise (ie, hypoxemia, pulmonary infiltrates, pericardial or pleural effusions) (10 mg BID for 3–5 days with a taper over 2 weeks). Consider interrupting ATRA therapy until hypoxia resolves.

**Acute Myeloid Leukemia**

**AML-1 through AML-6**

- Extensively revised by removing age as a determinant of induction treatment strategy, reclassification of certain risk groups, addition of new induction treatment regimens. Clarification of parameters for and timing of BM aspirate and biopsy following induction were also revised.

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UPDATES

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**Updates in Version 1.2023 of the NCCN Guidelines for Acute Myeloid Leukemia from Version 3.2022 include:**

**AML-7 through AML-8**
- Extensively revised to to provide recommendations for consolidation therapy based on age and risk group.

**AML-9**
- Maintenance Therapy
  - Patient with intermediate or adverse risk disease; treatment column, bullet 1 modified: Maintenance therapy with oral azacitidine ~~300 mg PO daily on days 1–14 of each 28-day cycle~~ until progression or unacceptable toxicity (category 1, preferred for age ≥55 yAML-
  - Patient with intermediate or adverse risk disease; treatment column, bullet 2 added: Maintenance therapy with HMA until progression or unacceptable toxicity: Azacitidine, Decitabine (category 2B)
  - Post allogeneic HCT, in remission, and history of FLT3-ITD; treatment column, maintenance treatment options added: Midostaurin (category 2B) and Gilteritinib (category 2B)
- References moved to the Principles of Systemic Therapy.

**AML-10**
- Footnote bbb modified: ~~Comprehensive~~ Multi-gene molecular profiling/targeted NGS (including IDH1/IDH2, FLT3 mutations) is suggested as it may assist with selection of therapy and appropriate clinical trials (see Discussion). Molecular testing should be repeated at each relapse or progression.

**AML-A 1 of 4**
- Page revised by updating table to 2022 ELN recommendations

**AML-A 4 of 4**
- Name of syndrome modified: Telomere syndromes due to mutation in TERC or TERT (OMIM 127550, 613989, and 615190)
- Causative Gene(s) for telomere syndromes due to mutation in TERC or TERT (OMIM 127550, 613989, and 615190) modified: TERC~~/~~,TERT and RTEL1

**AML-D**
- General supportive care, bullet 11 modified: Consider iron, folate, and vitamin B12 supplementation if deficient. Iron supplementation may be avoided in someone with excess iron levels.

**AML-E**
- Principles of Systemic Therapy added

**AML-F**
- General, sub-bullet 7 modified: In patients who develop cerebellar toxicity, cytarabine should be stopped. ~~The patient should not be rechallenged~~ Rechallenge with HiDAC in future treatment cycles should not be attempted

**AML-K 1 of 2**
- General
  - Bullet 2 added: Patients with disease in remission should take breaks between treatment, such as extending cycle length from 28-day to 42-day cycles.
  - Bullet 4, sub-bullet 1 added: Strong CYP3A4 inhibitors (especially posaconazole) require significant dose reductions during initiation and ramp-up phase followed by a reduced daily dose.
  - Bullet 4, sub-bullet 2 added: The use of strong or moderate CYP3A4 inducers (eg, carbamazepine, phenytoin, rifampin) should be avoided.

**BPDCN-1**
- Evaluation, bullet 5 modified: All patients require a diagnostic LP at the time of initial diagnosis, at disease relapse, or any other time when there is a clinical suspicion for CNS involvement. Follow with IT ~~treatment~~ chemotherapy prophylaxis as clinically indicated

**BPDCN-A**
- Footnote a added: Close collaboration with dermatology is recommended. For guidance on classification and measurement of skin lesions, see page MFSS-3 in the NCCN Guidelines for Primary Cutaneous Lymphomas

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## EVALUATION FOR AML

- History and physical (H&P)
- Complete blood count (CBC), platelets, differential, comprehensive metabolic panel (CMP), uric acid, lactate dehydrogenase (LDH)
- B12 and folic acid evaluation
- Prothrombin time (PT), partial thromboplastin time (PTT), fibrinogen
- Bone marrow (BM) core biopsy and aspirate analyses, including immunophenotyping by immunohistochemistry (IHC) stains + flow cytometry, and the analysis of chromosomal structural variations by cytogenetics, fluorescence in situ hybridization (FISH), or whole genome sequencing (See AML-A)
- Molecular analyses (*ASXL1*, c-*KIT*, *FLT3* [ITD (internal tandem duplication) and TKD (tyrosine kinase domain)], *NPM1*, *CEBPA* [biallelic], *IDH1*, *IDH2*, *RUNX1*, *TP53*, and other mutations[a] (See AML-A)
- Comprehensive pathology report, including diagnosis of AML (acute myeloid leukemia) with recurrent cytogenetics vs. AML not otherwise specified (NOS), blast count, cellularity, morphologic dysplasia, and mutation status if available
- Human leukocyte antigen (HLA) typing for patient with potential hematopoietic cell transplantation (HCT) in the future (except for patients with a major contraindication to HCT) and/or early referral to transplant center
- Brain CT without contrast, if central nervous system (CNS) hemorrhage suspected[b] (See AML-B)
- Brain MRI with contrast, if leukemic meningitis suspected[b] (See AML-B)
- PET/CT, if clinical suspicion for extramedullary disease (See AML-B)
- Lumbar puncture (LP), if symptomatic[b] (category 2B for asymptomatic)
- Evaluate myocardial function (echocardiogram or MUGA scan) in patients with a history or symptoms of cardiac disease or prior/planned exposure to cardiotoxic drugs or radiation therapy (RT) to thorax
- Consider early integration of palliative care[c] (See NCCN Guidelines for Palliative Care)

## DIAGNOSTIC STUDIES

Multidisciplinary diagnostic studies[d,e,j]

## DIAGNOSIS[d,e,f,j]

**Acute promyelocytic leukemia (APL):**
In patients with clinical or pathologic features of APL, start all-trans retinoic acid (ATRA) upon first suspicion of APL.[h] Early initiation of ATRA may prevent the lethal complication of bleeding.[h] If cytogenetic and molecular testing do not confirm APL, discontinue ATRA and continue treatment as for AML

→ See APL Classification and Treatment Recommendations (APL-1)

**AML:**
To appropriately stratify available intensive therapy options, expedite test results of molecular and cytogenetic analyses for immediately actionable mutations or chromosomal abnormalities (eg, core binding factor [CBF], *FLT3* [ITD and TKD], *NPM1*, *IDH1*, *IDH2*)

- For patients with hyperleukocytosis uncontrolled with hydroxyurea or leukapheresis, one dose of intermediate-dose cytarabine (1–2 g) may be considered prior to receiving diagnostic results[i]
- For patients who prefer not to receive blood transfusion(s), see AML-D for general considerations and supportive care

For suspicion of blastic plasmacytoid dendritic cell neoplasm (BPDCN), see BPDCN-INTRO

→ See AML Risk Stratification and Treatment Recommendations Risk Group and Induction (Intensive Induction Eligible) (AML-1)

**Myelodysplastic syndromes (MDS)** → See NCCN Guidelines for Myelodysplastic Syndromes

**B-cell or T-cell lymphoblastic leukemia/lymphoma[e]** → See NCCN Guidelines for Acute Lymphoblastic Leukemia

See footnotes on EVAL-1A

**Note: All recommendations are category 2A unless otherwise indicated.**
**Clinical Trials: NCCN believes that the best management of any patient with cancer is in a clinical trial. Participation in clinical trials is especially encouraged.**

## FOOTNOTES FOR EVALUATION FOR AML

[a] A variety of gene mutations are associated with specific prognoses (category 2A) and may guide medical decision-making (category 2B). Other genetic lesions may have therapeutic significance. The field of genomics in myeloid malignancies and related implications in AML are evolving rapidly. Mutations should be tested in all patients. Multiplex gene panels and targeted next-generation sequencing (NGS) analysis are recommended for the ongoing management of AML and various phases of treatment. (Papaemmanuil E, et al. N Engl J Med 2016;374:2209-2221; Lindsley RC, et al. Blood 2015;125:1367-1376; Dohner H, et al. Blood 2017;129:424-447) (see Discussion). If a test is not available at your institution, consult the pathology team (prior to performing the BM evaluation) about preserving material from the original diagnostic sample for future testing at an outside reference lab. Peripheral blood may alternatively be used to detect molecular abnormalities in patients with disease with morphologically detectable, circulating leukemic blasts.

[b] Consider administration of one dose of intrathecal (IT) chemotherapy (methotrexate or cytarabine) at time of diagnostic LP. See Evaluation and Treatment of CNS Leukemia (AML-B).

[c] El-Jawahri A, et al. JAMA Oncol 2021;7:238-245.

[d] Khoury JD, et al. Leukemia 2022;36:1703-1719.

[e] When presented with rare cases such as acute leukemias of ambiguous lineage (ALAL) including mixed phenotype acute leukemias (MPAL) (according to 2016 WHO classification), consultation with an experienced hematopathologist is strongly recommended.

[f] Young adults may be eligible for pediatric trials with more intensive induction regimens and transplant options. Patients with AML should preferably be cared for at experienced leukemia centers where clinical trials may be more available.

[h] ATRA should be available in all community hospitals, so appropriate therapy can be started promptly.

[i] Kim K, et al. Am J Hematol 2022;97:885-894.

[j] Arber DA, et al. Blood 2022;140:1200-1228.

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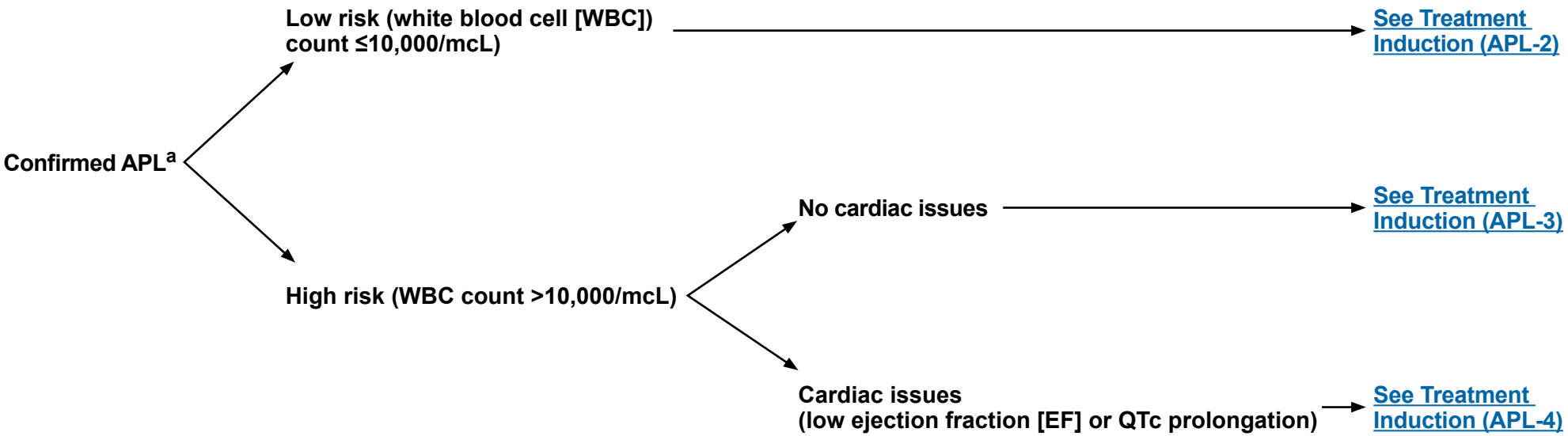
## APL CLASSIFICATION AND TREATMENT RECOMMENDATIONS




[a] Therapy-related APL is treated the same as de novo APL. FLT3 inhibitors are not recommended for *FLT3*-positive APL. Gale RE, et al. Blood 2005;106:3768-3776.

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**Clinical Trials: NCCN believes that the best management of any patient with cancer is in a clinical trial. Participation in clinical trials is especially encouraged.**

## APL TREATMENT INDUCTION (LOW RISK)[b,c,d,e]

### Preferred Regimens

**ATRA[f] 45 mg/m² in 2 divided doses daily + arsenic trioxide[g] 0.15 mg/kg IV daily[h] (category 1)** See Principles of Supportive Care for APL (APL-A)

- If blood count recovery by day 28 (platelet >100,000, absolute neutrophil count (ANC) >1,000), proceed with consolidation. BM aspirate and biopsy may be considered to document <5% blasts and no abnormal promyelocytes[l,m] but is optional
- If full course of induction treatment not given, or counts have not recovered by day 28–35, a BM aspirate and biopsy is recommended to document <5% blasts and no abnormal promyelocytes[l,m] before proceeding with consolidation

→ **Arsenic trioxide[g] 0.15 mg/kg/d IV 5 d/wk for 4 weeks every 8 weeks for a total of 4 cycles, and ATRA 45 mg/m²/d for 2 weeks every 4 weeks for a total of 7 cycles[h] (category 1)**

**or**

**ATRA[f] 45 mg/m² in 2 divided doses daily + arsenic trioxide[g] 0.3 mg/kg IV on days 1–5 of week 1 and 0.25 mg/kg twice weekly during weeks 2–8[i] (category 1)** See Principles of Supportive Care for APL (APL-A)

- If blood count recovery by day 28 (platelet >100,000, ANC >1,000), proceed with consolidation. BM aspirate and biopsy may be considered to document <5% blasts and no abnormal promyelocytes[l,m] but is optional
- If full course of induction treatment not given, or counts have not recovered by day 28–35, a BM aspirate and biopsy is recommended to document <5% blasts and no abnormal promyelocytes[l,m] before proceeding with consolidation

→ **First 3 consolidation cycles = 56-day cycles:**
**ATRA 45 mg/m²/d PO in 2 divided doses daily on days 1–14 and 29–42 (2 weeks on followed by 2 weeks off) + arsenic trioxide[g] 0.3 mg/kg on days 1–5 of week 1 followed by 0.25 mg/kg twice weekly during weeks 2–4[i]**
**4th consolidation cycle = 28-day cycle:**
**ATRA 45 mg/m²/d PO in 2 divided doses daily on days 1–14 (2 weeks on followed by 2 weeks off) + arsenic trioxide[g] 0.3 mg/kg on days 1–5 of week 1 followed by 0.25 mg/kg twice weekly during weeks 2–4[i]**

### Useful in Certain Circumstances (if arsenic is not available or contraindicated)

**ATRA[f] 45 mg/m² in 2 divided doses daily + idarubicin 12 mg/m² on days 2, 4, 6, 8[j] (category 1) or on days 2, 4, 6 for aged >70 y[h,j]**

→ **At count recovery, proceed with consolidation[m,n,o]** → **ATRA 45 mg/m² x 15 days + idarubicin 5 mg/m² x 4 days x 1 cycle, then ATRA x 15 days + mitoxantrone 10 mg/m²/d x 3 days x 1 cycle, then ATRA x 15 days + idarubicin 12 mg/m² x 1 day x 1 cycle (category 1)[j]**

**or**

**ATRA[f] 45 mg/m² in 2 divided doses daily + a single dose of gemtuzumab ozogamicin 9 mg/m² on day 5[k]**

→ **BM aspirate and biopsy days 28–35 to document <5% blasts and no abnormal promyelocytes[m] before proceeding with consolidation** → **ATRA 45 mg/m² in 2 divided doses daily during weeks 1–2, 5–6, 9–10, 13–14, 17–18, 21–22, and 25–26. A single dose of gemtuzumab ozogamicin 9 mg/m² may be given monthly[k] until achievement of complete molecular response**

## CONSOLIDATION THERAPY[m,n]

→ See Post-Consolidation Therapy (APL-5)

See footnotes on APL-2A

**Note: All recommendations are category 2A unless otherwise indicated.**
**Clinical Trials: NCCN believes that the best management of any patient with cancer is in a clinical trial. Participation in clinical trials is especially encouraged.**

## FOOTNOTES FOR APL TREATMENT INDUCTION AND CONSOLIDATION THERAPY (LOW RISK)

[b] Several groups have published large trials with excellent outcomes. However, to achieve the expected results, one needs to use the regimen consistently through all components and not mix induction from one trial with consolidation from another.
[c] Monitor for APL differentiation syndrome and coagulopathy; see Principles of Supportive Care for APL (APL-A).
[d] Early mortality is related to bleeding, differentiation syndrome, or infection. Persistent disease is rare.
[e] Hydroxyurea should be considered to manage high WBC count (>10,000/mcL) during induction with ATRA/arsenic trioxide.
[f] Data suggest that lower doses of ATRA (25 mg/m$^2$) in divided doses until clinical remission may be used in children and adolescents. Kutny MA, et al. J Clin Oncol 2017;35:3021-3029.
[g] QTc and monitoring and optimizing electrolytes are important in safe administration of arsenic trioxide. See Arsenic trioxide monitoring in Principles of Supportive Care for APL (APL-A). Electrocardiogram (ECG) is recommended prior to initiating arsenic trioxide. During therapy, if a patient presents with a prolonged QT interval, the use of QTcF correction formula is recommended. Interventions such as minimizing concurrent QT-prolonging drugs and electrolyte correction are recommended prior to discontinuing arsenic trioxide.
[h] Lo-Coco F, et al. N Engl J Med 2013;369:111-121. Begin prophylaxis with prednisone; the optimal duration of steroid prophylaxis is unknown. If differentiation syndrome develops, change to dexamethasone. See Principles of Supportive Care for APL (APL-A).
[i] Burnett AK, et al. Lancet Oncol 2015;16:1295-1305.
[j] Sanz MA, et al. Blood 2010;115:5137-5146.
[k] Estey E, et al. Blood 2002;99:4222-4224.
[l] If no evidence of morphologic disease (<5% blasts and no abnormal promyelocytes), discontinue ATRA and arsenic trioxide to allow for peripheral blood recovery since arsenic trioxide can be associated with significant myelosuppression. If evidence of morphologic disease, continue ATRA and arsenic trioxide and repeat BM 1 week later.
[m] The presence of measurable cytogenetic and molecular markers does not carry prognostic or therapeutic implications.
[n] For regimens using high cumulative doses of cardiotoxic agents, consider reassessing cardiac function prior to each anthracycline/mitoxantrone-containing course.
[o] If full course of induction not given, BM biopsy should still be performed.

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## APL TREATMENT INDUCTION (HIGH RISK)[b,c,d,p,q]

(For patients with cardiac issues, see APL-4)

**Preferred Regimens**

ATRA[f] 45 mg/m² (days 1–36, 2 divided doses daily) + age-adjusted idarubicin 6–12 mg/m² on days 2, 4, 6, 8 + arsenic trioxide[g] 0.15 mg/kg (days 9–36 as 2 h IV infusion)[r]

→ BM aspirate and biopsy at day 28 to document remission,[l,m] consider LP before proceeding with consolidation[w]

→ ATRA 45 mg/m² x 28 days + arsenic trioxide[g] 0.15 mg/kg/d x 28 days x 1 cycle, then ATRA 45 mg/m² x 7 days every 2 weeks x 3 + arsenic trioxide 0.15 mg/kg/d x 5 days for 5 weeks x 1 cycle[r,x,y]

or

ATRA[f] 45 mg/m² in 2 divided doses daily and arsenic trioxide[g] 0.15 mg/kg/d IV + a single dose of gemtuzumab ozogamicin 9 mg/m² may be given on day 1, or day 2, or day 3, or day 4[s]

→ BM aspirate and biopsy at day 28 to document remission,[l,m] consider LP before proceeding with consolidation[w]

→ Arsenic trioxide[g] 0.15 mg/kg daily 5 d/wk for 4 weeks every 8 weeks for a total of 4 cycles + ATRA 45 mg/m² for 2 weeks every 4 weeks for a total of 7 cycles.[s,y] If ATRA or arsenic trioxide discontinued due to toxicity, a single dose of gemtuzumab ozogamicin 9 mg/m² may be given every 4–5 weeks provided platelets and ANC recover to ≥100 and ≥1.0, respectively, until molecular complete response (CR)[k]

or

ATRA[f] 45 mg/m² in 2 divided doses daily and arsenic trioxide[g] 0.3 mg/kg IV on days 1–5 of week 1 and 0.25 mg/kg twice weekly on weeks 2–8 (category 1) + a single dose of gemtuzumab ozogamicin 6 mg/m² may be given on day 1, or day 2, or day 3, or day 4[l]

→ BM aspirate and biopsy at day 28 to document remission,[l,m] consider LP before proceeding with consolidation[w]

→ ATRA 45 mg/m² for 2 weeks every 4 weeks (or for 2 weeks on 2 weeks off) in consolidation courses 1–4 + arsenic trioxide[g] 0.3 mg/kg on days 1–5 of week 1 in consolidation courses 1–4 and 0.25 mg/kg twice weekly in weeks 2–4 in consolidation courses 1–4 (category 1).[i,y] If ATRA or arsenic trioxide discontinued due to toxicity, a single dose of gemtuzumab ozogamicin 9 mg/m² may be given every 4–5 weeks provided platelets and ANC recover to ≥100 and ≥1.0, respectively, until molecular CR[k]

**Other Recommended Regimens[t]**

ATRA[f] 45 mg/m² in 2 divided doses daily + daunorubicin 50 mg/m² x 4 days (IV days 3–6) + cytarabine 200 mg/m² x 7 days (IV days 3–9)[u]

→ BM aspirate and biopsy at day 28 to document remission,[l] consider LP before proceeding with consolidation[w]

→ Arsenic trioxide[g] 0.15 mg/kg/d x 5 days for 5 weeks every 7 weeks for a total of 2 cycles, then ATRA 45 mg/m² x 7 days + daunorubicin 50 mg/m² x 3 days for 2 cycles[u,y]

or

ATRA[f] 45 mg/m² in 2 divided doses daily + daunorubicin 60 mg/m² x 3 days + cytarabine 200 mg/m² x 7 days[v]

→ BM aspirate and biopsy at day 28 to document remission,[m] consider LP before proceeding with consolidation[w]

→ Daunorubicin 60 mg/m² x 3 days + cytarabine 200 mg/m² x 7 days x 1 cycle, then cytarabine [2 g/m² (aged <50 y) or 1.5 g/m² (aged 50–60 y) every 12 h x 5 days[x,z] or 1 g/m² (aged >60 y) every 12 h x 4 days] + daunorubicin 45 mg/m² x 3 days x 1 cycle + 5 doses of IT chemotherapy[v]

or

ATRA[f] 45 mg/m² in 2 divided doses daily + idarubicin 12 mg/m² on days 2, 4, 6, 8[j] or on days 2, 4, 6 for those aged >70 y

→ BM aspirate and biopsy at day 28 to document remission,[m] consider LP before proceeding with consolidation[w]

→ ATRA 45 mg/m² x 15 days + idarubicin 5 mg/m² and cytarabine 1 g/m² x 4 days x 1 cycle,[aa] then ATRA x 15 days + mitoxantrone 10 mg/m²/d x 5 days[bb] x 1 cycle, then ATRA x 15 days + idarubicin 12 mg/m² x 1 day + cytarabine 150 mg/m²/8 h x 4 days x 1 cycle[j,y,aa]

See footnotes on APL-3A

## CONSOLIDATION THERAPY[n]

See references for details on regimens including maintenance therapy.

See Post-Consolidation Therapy (APL-5)

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## FOOTNOTES FOR APL TREATMENT INDUCTION AND CONSOLIDATION THERAPY (HIGH RISK)

[b] Several groups have published large trials with excellent outcomes. However, to achieve the expected results, one needs to use the regimen consistently through all components and not mix induction from one trial with consolidation from another.
[c] Monitor for APL differentiation syndrome and coagulopathy; see Principles of Supportive Care for APL (APL-A).
[d] Early mortality is related to bleeding, differentiation syndrome, or infection. Persistent disease is rare.
[f] Data suggest that lower doses of ATRA (25 mg/m$^2$) in divided doses until clinical remission may be used in children and adolescents. Kutny MA, et al. J Clin Oncol 2017;35:3021-3029.
[g] QTc and monitoring and optimizing electrolytes are important in safe administration of arsenic trioxide. See Arsenic trioxide monitoring in Principles of Supportive Care for APL (APL-A). ECG is recommended prior to initiating arsenic trioxide. During therapy, if a patient presents with a prolonged QT interval, the use of QTcF correction formula is recommended. Interventions such as minimizing concurrent QT-prolonging drugs and electrolyte correction are recommended prior to discontinuing arsenic trioxide.
[i] Burnett AK, et al. Lancet Oncol 2015;16:1295-1305.
[j] Sanz MA, et al. Blood 2010;115:5137-5146.
[k] Estey E, et al. Blood 2002;99:4222-4224.
[l] If no evidence of morphologic disease (<5% blasts and no abnormal promyelocytes), discontinue ATRA and arsenic trioxide to allow for peripheral blood recovery since arsenic trioxide can be associated with significant myelosuppression. If evidence of morphologic disease, continue ATRA and arsenic trioxide and repeat BM 1 week later.
[m] The presence of measurable cytogenetic and molecular markers does not carry prognostic or therapeutic implications.
[n] For regimens using high cumulative doses of cardiotoxic agents, consider reassessing cardiac function prior to each anthracycline/mitoxantrone-containing course.
[p] For patients with a high WBC count (>10,000/mcL), prophylactic steroids should be initiated to prevent differentiation syndrome (see Principles of Supportive Care for APL [APL-A]). The use of prednisone versus dexamethasone is protocol dependent.
[q] It is important for the management of APL that regimens containing ATRA and arsenic trioxide be administered unless there is a contraindication based on extenuating patient circumstances.
[r] Iland HJ, et al. Blood 2012;120:1570-1580.
[s] Abaza Y, et al. Blood 2017;129:1275-1283.
[t] No arsenic is included in induction if unavailable or contraindicated.
[u] Powell BL, et al. Blood 2010;116:3751-3757.
[v] Adès L, et al. Blood 2008;111:1078-1084.
[w] Breccia M, et al. Br J Haematol 2003;120:266-270.
[x] Although the original regimen included high-dose cytarabine (HiDAC) as second consolidation, some investigators recommend using HiDAC early for CNS prophylaxis, especially for patients not receiving IT chemotherapy.
[y] Consider IT chemotherapy (eg, 2 doses for each consolidation cycle) as an option for CNS prophylaxis.
[z] Dose adjustment of cytarabine may be needed for patients >60 years or patients with renal dysfunction.
[aa] High-risk patients who are >60 years did not receive cytarabine in consolidation and were treated as intermediate-risk patients in the LPA2005 study.
[bb] Mitoxantrone was reduced to 3 days in intermediate-risk patients in the LPA2005 study.

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## APL TREATMENT INDUCTION (HIGH RISK)[b,c,d,p] IN PATIENTS WITH CARDIAC ISSUES

(For patients without cardiac issues, see APL-3)

### Low EF

ATRA[f] 45 mg/m² in 2 divided doses daily + arsenic trioxide[g] 0.15 mg/kg daily + a single dose of gemtuzumab ozogamicin 9 mg/m² on day 1[s]

→ BM aspirate and biopsy at day 28 to document remission[l,m] before proceeding with consolidation

→ Arsenic trioxide[g] 0.15 mg/kg daily 5 days/wk for 4 weeks every 8 weeks for a total of 4 cycles + ATRA 45 mg/m² in 2 divided doses daily for 2 weeks every 4 weeks for a total of 7 cycles.[s,y] If ATRA or arsenic trioxide discontinued due to toxicity, a single dose of gemtuzumab ozogamicin 9 mg/m² may be given every 4–5 weeks provided platelets and ANC recover to ≥100 and ≥1.0, respectively, until molecular CR[k]

or

ATRA[f] 45 mg/m² in 2 divided doses daily + arsenic trioxide[g] 0.3 mg/kg on days 1–5 of week 1 and 0.25 mg/kg twice weekly in weeks 2–8[i] (category 1) + a single dose of gemtuzumab ozogamicin 6 mg/m² on day 1[i]

→ BM aspirate and biopsy at day 28 to document remission[l,m] before proceeding with consolidation

→ ATRA 45 mg/m² in 2 divided doses daily for 2 weeks every 4 weeks (or for 2 weeks on 2 weeks off) in consolidation courses 1–4 + arsenic trioxide[g] 0.3 mg/kg on days 1–5 of week 1 in consolidation courses 1–4 and 0.25 mg/kg twice weekly on weeks 2–4 in consolidation courses 1–4 (category 1).[i,y] If ATRA or arsenic trioxide discontinued due to toxicity, a single dose of gemtuzumab ozogamicin 9 mg/m² may be given every 4–5 weeks provided platelets and ANC recover to ≥100 and ≥1.0, respectively, until molecular CR[k]

### Prolonged QTc

ATRA[f] 45 mg/m² in 2 divided doses daily + a single dose of gemtuzumab ozogamicin 9 mg/m² on day 1[k]

→ BM aspirate and biopsy at day 28 to document remission[m] before proceeding with consolidation

→ ATRA 45 mg/m² in 2 divided doses daily during weeks 1–2, 5–6, 9–10, 13–14, 17–18, 21–22, and 25–26. Gemtuzumab ozogamicin 9 mg/m² may be given monthly[k] until molecular CR

or

ATRA[f] 45 mg/m² in 2 divided doses daily + daunorubicin 60 mg/m² x 3 days + cytarabine 200 mg/m² x 7 days[v]

→ BM aspirate and biopsy at day 28 to document remission,[m] consider LP before proceeding with consolidation[w]

→ Daunorubicin 60 mg/m² x 3 days + cytarabine 200 mg/m² x 7 days x 1 cycle, then cytarabine [2 g/m² (aged <50 y) or 1.5 g/m² (age 50–60 y) every 12 h x 5 days[x,z] or 1 g/m² (aged >60 y) every 12 h x 4 days], + daunorubicin 45 mg/m² x 3 days x 1 cycle + 5 doses of IT chemotherapy[v]

or

ATRA[f] 45 mg/m² in 2 divided doses daily + idarubicin 12 mg/m² on days 2, 4, 6, 8 or on days 2, 4, 6 for those aged >70 y[j]

→ BM aspirate and biopsy at day 28 to document remission,[m] consider LP before proceeding with consolidation[w]

→ ATRA 45 mg/m² x 15 days + idarubicin 5 mg/m² and cytarabine 1 g/m² x 4 days x 1 cycle,[aa] then ATRA x 15 days + mitoxantrone 10 mg/m²/d x 5 days[bb] x 1 cycle, then ATRA x 15 days + idarubicin 12 mg/m² x 1 day + cytarabine 150 mg/m²/8 h x 4 days x 1 cycle[j,c,aa]

## CONSOLIDATION THERAPY[n]

→ See Post-Consolidation Therapy (APL-5)

See footnotes on APL-4A

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## FOOTNOTES FOR APL TREATMENT INDUCTION AND CONSOLIDATION THERAPY (HIGH RISK)

[b] Several groups have published large trials with excellent outcomes. However, to achieve the expected results, one needs to use the regimen consistently through all components and not mix induction from one trial with consolidation from another.

[c] Monitor for APL differentiation syndrome and coagulopathy; see Principles of Supportive Care for APL (APL-A).

[d] Early mortality is related to bleeding, differentiation syndrome, or infection. Persistent disease is rare.

[f] Data suggest that lower doses of ATRA (25 mg/m$^2$) in divided doses until clinical remission may be used in children and adolescents. Kutny MA, et al. J Clin Oncol 2017;35:3021-3029.

[g] QTc and monitoring and optimizing electrolytes are important in safe administration of arsenic trioxide. See Arsenic trioxide monitoring in Principles of Supportive Care for APL (APL-A). ECG is recommended prior to initiating arsenic trioxide. During therapy, if a patient presents with a prolonged QT interval, the use of QTcF correction formula is recommended. Interventions such as minimizing concurrent QT-prolonging drugs and electrolyte correction are recommended prior to discontinuing arsenic trioxide.

[i] Burnett AK, et al. Lancet Oncol 2015;16:1295-1305.

[j] Sanz MA, et al. Blood 2010;115:5137-5146.

[k] Estey E, et al. Blood 2002;99:4222-4224.

[l] If no evidence of morphologic disease (<5% blasts and no abnormal promyelocytes), discontinue ATRA and arsenic trioxide to allow for peripheral blood recovery since arsenic trioxide can be associated with significant myelosuppression. If evidence of morphologic disease, continue ATRA and arsenic trioxide and repeat BM 1 week later.

[m] The presence of measurable cytogenetic and molecular markers does not carry prognostic or therapeutic implications.

[n] For regimens using high cumulative doses of cardiotoxic agents, consider reassessing cardiac function prior to each anthracycline/mitoxantrone-containing course.

[p] For patients with a high WBC count (>10,000/mcL), prophylactic steroids should be initiated to prevent differentiation syndrome (see Principles of Supportive Care for APL [APL-A]). The use of prednisone versus dexamethasone is protocol dependent.

[s] Abaza Y, et al. Blood 2017;129:1275-1283.

[v] Adès L, et al. Blood 2008;111:1078-1084.

[w] Breccia M, et al. Br J Haematol 2003;120:266-270.

[x] Although the original regimen included HiDAC as second consolidation, some investigators recommend using HiDAC early for CNS prophylaxis, especially for patients not receiving IT chemotherapy.

[y] Consider 4–6 doses of IT chemotherapy (eg, 2 doses for each consolidation cycle) as an option for CNS prophylaxis.

[z] Dose adjustment of cytarabine may be needed for patients >60 years or patients with renal dysfunction.

[aa] High-risk patients who are >60 years did not receive cytarabine in consolidation and were treated as intermediate-risk patients in the LPA2005 study.

[bb] Mitoxantrone was reduced to 3 days in intermediate-risk patients in the LPA2005 study.

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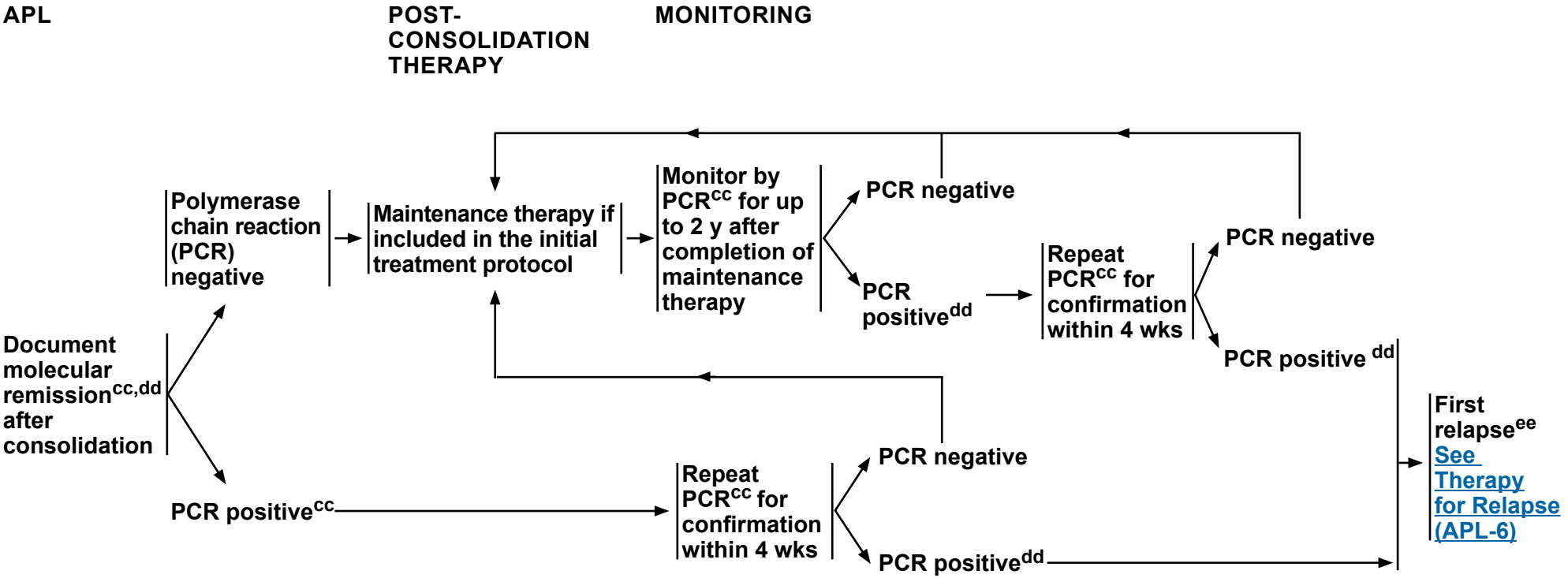


[cc] PCR should be performed on a blood sample at completion of consolidation to document molecular remission. In patients receiving the ATRA/arsenic regimen, consider earlier sampling at 3–4 months during consolidation. Prior practice guidelines have recommended monitoring blood by PCR every 3 mo for 2 y to detect molecular relapse. We continue to endorse this for patients with high-risk disease, those >60 y of age or who had long interruptions during consolidation, or patients on regimens that use maintenance and are not able to tolerate maintenance. Clinical experience indicates that risk of relapse in patients with low-risk disease who are in molecular remission at completion of consolidation is low and monitoring may not be necessary outside the setting of a clinical trial. While long-term monitoring has been standard, with newer, more effective regimens, the value is less certain.

[dd] To confirm PCR positivity, a second blood sample should be done in 2–4 weeks in a reliable laboratory. If molecular relapse is confirmed by a second positive test, treat as first relapse (APL-6). If the second test is negative, frequent monitoring (every 3 mo for 2 y) is strongly recommended to confirm that the test remains negative. The PCR testing lab should indicate the level of sensitivity of assay for positivity (most clinical labs have a sensitivity level of $10^{-4}$), and testing should be done in the same lab to maintain the same level of sensitivity. Consider consultation with a physician experienced in molecular diagnostics if results are equivocal.

[ee] Grimwade D, et al. J Clin Oncol 2009;27:3650-3658.

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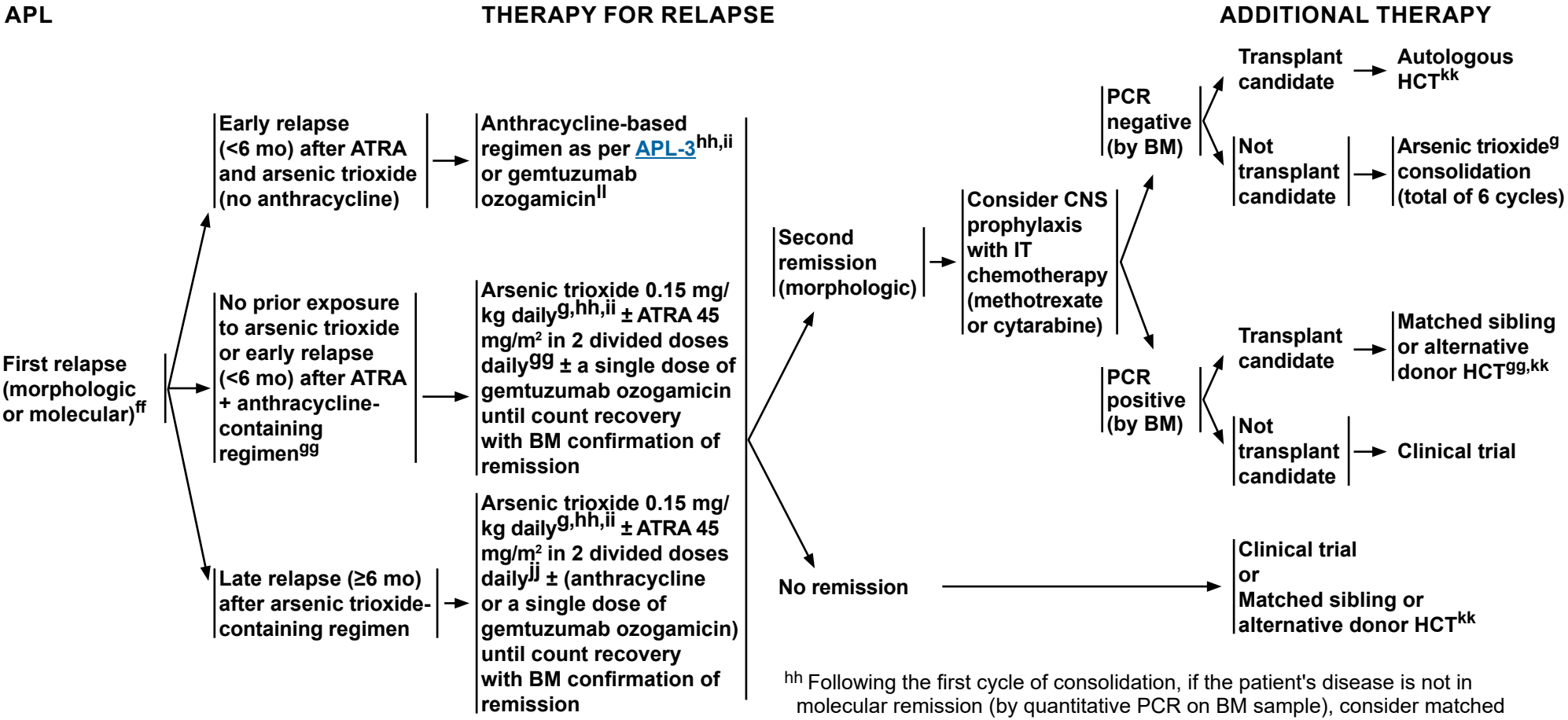


g QTc and monitoring and optimizing electrolytes are important in safe administration of arsenic trioxide. See Arsenic trioxide monitoring in Principles of Supportive Care for APL (APL-A). ECG is recommended prior to initiating arsenic trioxide. During therapy, if a patient presents with a prolonged QT interval, the use of QTcF correction formula is recommended. Interventions such as minimizing concurrent QT-prolonging drugs and electrolyte correction are recommended prior to discontinuing arsenic trioxide.

ff Document molecular panel to verify relapsed APL versus therapy-related AML.

gg Cicconi L, et al. Ann Hematol 2018;97:1797-1802.

hh Following the first cycle of consolidation, if the patient's disease is not in molecular remission (by quantitative PCR on BM sample), consider matched sibling or alternative donor (haploidentical, unrelated donor, or cord blood) HCT or clinical trial. Testing is recommended at least 2–3 weeks after the completion of arsenic trioxide to avoid false positives.

ii Outcomes are uncertain in patients who received arsenic trioxide during initial induction/consolidation therapy.

jj There is a small randomized trial that suggests that the addition of ATRA does not confer any benefit over arsenic trioxide alone. Raffoux E, et al. J Clin Oncol 2003;21:2326-2334.

kk See NCCN Guidelines for Hematopoietic Cell Transplantation.

ll Lo-Coco F, et al. Blood 2004;104:1995-1999.

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## PRINCIPLES OF SUPPORTIVE CARE FOR APL[a]

**There are variations among institutions, but the following issues are important to consider in the management of APL.**

- **Clinical coagulopathy:**
  - **Management of clinical coagulopathy: Aggressive platelet transfusion support to maintain platelets ≥50,000/mcL; fibrinogen replacement with cryoprecipitate and fresh frozen plasma to maintain a level >150 mg/dL and PT and PTT close to normal values. Monitor daily until coagulopathy resolves.**
  - **Avoid use of tunneled catheter or port-a-cath.**
- **Leukapheresis[1] is not routinely recommended in patients with a high WBC count in APL because of the difference in leukemia biology; however, in life-threatening cases with leukostasis that is not responsive to other modalities, leukapheresis can be considered with caution.**
- **APL differentiation syndrome:**
  - **Maintain a high index of suspicion of APL differentiation syndrome (ie, fever, often associated with increasing WBC count >10,000/mcL, usually at initial diagnosis or relapse; shortness of breath; hypoxemia; pleural or pericardial effusions).[2] Close monitoring of volume overload and pulmonary status is indicated. Initiate dexamethasone at first signs or symptoms of respiratory compromise (ie, hypoxemia, pulmonary infiltrates, pericardial or pleural effusions) (10 mg BID for 3–5 days with a taper over 2 weeks). Consider interrupting ATRA therapy until hypoxia resolves.**

**For patients at high risk (WBC count >10,000/mcL) for developing differentiation syndrome, initiate prophylaxis with corticosteroids, either prednisone 0.5 mg/kg day 1 or dexamethasone 10 mg every 12 h (See NCCN Guidelines for Prevention and Treatment of Cancer-Related Infections). Taper the steroid dose over a period of several days. If patient develops differentiation syndrome, change prednisone to dexamethasone 10 mg every 12 h until count recovery or risk of differentiation has abated.[2,3]**

- **The following cytoreduction strategies for leukocytosis may be used for differentiation syndrome that is difficult to treat: hydroxyurea, anthracycline, or gemtuzumab ozogamicin.**

- **Arsenic trioxide monitoring:**
  - **Prior to initiating therapy**
    - ◊ **ECG for prolonged QTc interval assessment**
    - ◊ **Serum electrolytes (Ca, K, Mg, phosphorus) and creatinine**
  - **During therapy (weekly during induction therapy and before each course of post-remission therapy)**
    - ◊ **Minimize use of drugs that may prolong QT interval.**
    - ◊ **Maintain K and Mg concentrations within middle or upper range of normal.**
    - ◊ **In patients with prolonged QTc interval >500 millisec, correct electrolytes and proceed with caution. QTcF is recommended; however, in settings where QTcF corrections are unavailable, a cardiology consult may be appropriate for patients with prolonged QTc.[4]**
- **Myeloid growth factors should not be used during induction. They may be considered during consolidation in selected cases (ie, life-threatening infections, signs/symptoms of sepsis); however, there are no outcomes data regarding the prophylactic use of growth factors in consolidation.**

[a] Antiviral prophylaxis zoster for duration of treatment may be appropriate. Freyer CW, et al. Leuk Lymphoma 2021;62:696-702; Glass JL, et al. Blood 2015;126:Abstract 3752.

[1] Daver N, et al. Br J Haematol 2015;168:646-653.
[2] Lo-Coco F, et al. N Engl J Med 2013;369:111-121.
[3] Sanz MA, et al. Blood 2010;115:5137-5146.
[4] Sanz MA, et al. Blood 2019;133:1630-1643.

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# NCCN Guidelines Version 3.2023
# Acute Myeloid Leukemia (Age ≥18 years)

NCCN Guidelines Index
Table of Contents
Discussion

**INTENSIVE INDUCTION ELIGIBLE**

**Induction eligible**[a,b]

**RISK GROUP**

**Favorable-risk AML (CBF-AML,**[c] ***NPM1*****-mutated/*****FLT3*** **wild-type AML, in-frame basic leucine zipper [bZIP] mutation in *CEBPA*)**[y]

**TREATMENT INDUCTION**[e,f,g,h,t]
**Principles of Venetoclax, see AML-K**

**Preferred:**
- **Standard 7+3 (daunorubicin)**[k,l,u,v] **+ gemtuzumab ozogamicin**[d,i] **(CD33 positive)**[j]

**Other Recommended:**
- **Standard 7+3 (daunorubicin or idarubicin)**[k,l,u,v]
- **7+3 (mitoxantrone)**[k,l,u,v] **(for age ≥60 y)**
- **FLAG-IDA (fludarabine + HiDAC**[z] **+ granulocyte colony-stimulating factor [G-CSF]**[m] **- idarubicin) + gemtuzumab ozogamicin**[d,i] **(category 2B; use with caution in patients >60 y)**

**AML with *FLT3*-ITD/TKD mutation** → **Standard 7+3 (daunorubicin)**[k,l,u,v] **+ midostaurin**[n,w]

**Intermediate-risk AML**

**Preferred:**
- **Standard 7+3 (daunorubicin or idarubicin)**[k,l,u,v] **(category 1)**
- **7+3 (mitoxantrone)**[k,l,u,v] **(for age ≥60 y)**

**Other Recommended:**
- **Standard 7+3 (daunorubicin)**[k,l,u,v] **+ gemtuzumab ozogamicin**[i] **(CD33 positive)**[j]
- **FLAG-IDA**[m,z] **± gemtuzumab ozogamicin**[i] **(category 2B; use with caution in patients >60 y)**
- **FLAG-IDA**[m,s] **+ venetoclax (category 3)**

**Poor risk groups** → **See AML-2**

See Follow-Up and Re-Induction After Standard-Dose Cytarabine Induction (AML-3)

See AML-5 (Intensive Induction Ineligible)

See footnotes on AML-2A

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**INTENSIVE INDUCTION ELIGIBLE**

**RISK GROUP**

**TREATMENT INDUCTION[f,g,h,e,t]**
**Principles of Venetoclax, see AML-K**

**Induction eligible[a,b]**

**Favorable and intermediate risk groups** → **See AML-1**

**Poor-risk AML with and without *TP53* mutation or del17p abnormality[o,x]**

- Standard 7+3 (idarubicin or daunorubicin)[k,l,u,v] (category 1)
- 7+3 (mitoxantrone)[k,l,u,v] (for age ≥60 y)
- HiDAC[l,z,aa] + idarubicin or daunorubicin[u,v] + etoposide (category 1 for patients ≤45 y, category 2B for other age groups)
- FLAG-IDA[m,z] (category 2B)
- FLAG-IDA[m,s] + venetoclax (category 3)
- Decitabine (days 1–5) + venetoclax[q]
- Decitabine (days 1–10) + venetoclax[q] (category 3)
- Azacitidine + venetoclax[q]
- Low-dose cytarabine (LDAC) + venetoclax[q]
- Low-intensity therapy (azacitidine [category 2B] or decitabine)

**Therapy-related AML other than CBF-AML**
**Antecedent MDS/chronic myelomonocytic leukemia (CMML)**
**Cytogenetic changes consistent with MDS (AML with myelodysplasia-related changes [AML-MRC])[x]**

- Standard 7+3 (daunorubicin or idarubicin)[k,l,u,v] (category 1)
- CPX-351/dual-drug liposomal cytarabine and daunorubicin[p] (category 1 for ≥60 y, category 2B for <60 y)
- Decitabine (days 1–5) + venetoclax[q,r]
- Azacitidine + venetoclax[q,r]
- LDAC + venetoclax[q]
- Low-intensity therapy (azacitidine or decitabine)[r]

→ See Follow-Up and Re-Induction After Standard-Dose Cytarabine Induction (AML-3)
or
Follow-Up After High-Dose Cytarabine Induction for Poor-Risk AML (AML-4)

See footnotes on AML-2A

**Note: All recommendations are category 2A unless otherwise indicated.**
**Clinical Trials: NCCN believes that the best management of any patient with cancer is in a clinical trial. Participation in clinical trials is especially encouraged.**

## FOOTNOTES FOR INTENSIVE INDUCTION ELIGIBLE

[a] Patients with elevated blast counts are at risk for tumor lysis and organ dysfunction secondary to leukostasis. Measures to rapidly reduce the WBC count include leukapheresis, hydroxyurea, and/or a single dose of cytarabine (1–2 g). Prompt institution of definitive therapy is essential.

[b] Poor performance/functional status and a comorbid medical condition, in addition to age, are factors that influence ability to tolerate standard induction therapy. Web-based tools available to evaluate the probability of CR and early death after standard induction therapy in patients aged ≥60 years with AML can be found at: Walter RB, et al. J Clin Oncol 2011;29:4417-4423; Borlenghi E, et al. J Geriatr Oncol 2021;12:550-556. See NCCN Guidelines for Older Adult Oncology.

[c] Consider screening with FISH to identify translocations/abnormalities associated with CBF-AML.

[d] For CBF-AML with *FLT3* mutation, the panel prefers gemtuzumab ozogamicin. Gemtuzumab ozogamicin may be beneficial in *NPM1*-mutated AML (Kapp-Schwoerer S, et al. Blood 2020;136:3041-3050). The role of gemtuzumab ozogamicin in *CEBPA*-mutated AML is not established.

[e] See Principles of Supportive Care for AML (AML-F).

[f] See Monitoring During Therapy (AML-G).

[g] Consider referral to palliative care for consultation at the start of induction. LeBlanc TW, et al. Curr Hematol Malig Rep 2017;12:300-308 and LeBlanc TW, et al. J Oncol Pract 2017;13:589-590. See NCCN Guidelines for Palliative Care.

[h] See General Considerations and Supportive Care for Patients with AML Who Prefer Not to Receive Blood Transfusions (AML-D).

[i] Patients who receive transplant shortly following gemtuzumab ozogamicin administration may be at risk for developing sinusoidal obstruction syndrome (SOS). Wadleigh M, et al. Blood 2003;102:1578-1582. If transplant is planned, note that prior studies have used a 60- to 90-day interval between the last administration of gemtuzumab ozogamicin and HCT.

[j] Threshold for CD33 is not well-defined and may be ≥1%.

[k] ECOG reported a significant increase in CR rates and overall survival (OS) using daunorubicin 90 mg/m$^2$ x 3 days versus 45 mg/m$^2$ x 3 days in patients <60 years of age. Fernandez HF, et al. N Engl J Med 2009;361:1249-1259. If there is residual disease on days 12–14, the additional daunorubicin dose is 45 mg/m$^2$ x 3 days. Burnett AK, et al. Blood 2015;125:3878-3885.

[l] For patients with impaired cardiac function, other cytarabine-based regimens alone or with other agents can be considered. See Discussion.

[m] An FDA-approved biosimilar is an appropriate substitute for filgrastim.

[n] While midostaurin is not FDA approved for maintenance therapy, the study was designed for consolidation and maintenance midostaurin for a total of 12 months. Stone RM, et al. N Engl J Med 2017;377:454-464.

[o] Outcomes for patients with poor-risk AML with *TP53* mutation remain poor with conventional induction chemotherapy (Rücker FG, et al. Blood 2012;119:2114-2121) and the panel prioritizes clinical trial enrollment in this setting. While conventional induction chemotherapy regimens can be given in the setting of a *TP53* mutation, less intensive chemotherapy is preferred for patients not enrolled in clinical trials. (DiNardo CD, et al. N Engl J Med 2020;383:617-629;Welch JS, et al. N Engl J Med 2016;375:2023-2036).

[p] There are limited data supporting the use of this regimen in patients aged <60 years. Lancet JE, et al. J Clin Oncol 2018;36:2684-2692. For patients with AML-MRC and previous hypomethylating agent (HMA) exposure, the benefit from standard induction did not differ from the benefit with CPX-351/dual-drug liposomal encapsulation of cytarabine and daunorubicin.

[q] Venetoclax with decitabine, azacitidine, or LDAC may be continued for patients whose disease demonstrates clinical improvement (CR/CR with incomplete hematologic recovery [CRi]), with consideration of subsequent transplant, where appropriate. DiNardo CD, et al. Lancet Oncol 2018;19:216-228; Wei A, et al. Blood 2017;130:890; DiNardo CD, et al. Blood 2019;133:7-17; DiNardo CD, et al. N Engl J Med 2020;383:617-629.

[r] Patients whose disease has progressed to AML from MDS after significant exposure to HMAs (ie, azacitidine, decitabine) may be less likely to derive benefit from continued treatment with HMAs compared to patients who are HMA-naïve. Alternative treatment strategies should be considered.

[s] Doses of cytarabine should be modified based on age and renal insufficiency as per protocol. DiNardo CD, et al. J Clin Oncol 2021;39:2768-2778.

[t] See Principles of Systemic Therapy (AML-E).

Continued

**Note: All recommendations are category 2A unless otherwise indicated.**
**Clinical Trials: NCCN believes that the best management of any patient with cancer is in a clinical trial. Participation in clinical trials is especially encouraged.**

## FOOTNOTES FOR INTENSIVE INDUCTION ELIGIBLE

[u] For patients who exceed anthracycline dose or have cardiac issues but are still able to receive aggressive therapy, alternative non-anthracycline–containing regimens may be considered (eg, FLAG, clofarabine-based regimens [category 3]).

[v] The CR rates and 2-year OS in patients between 60 and 65 years of age treated with daunorubicin 90 mg/m$^2$ is also comparable to the outcome for idarubicin 12 mg/m$^2$; the higher-dose daunorubicin did not benefit patients >65 years of age (Löwenberg B, et al. N Engl J Med 2009;361:1235-1248).

[w] The RATIFY trial studied patients aged 18–60 y with *FLT3*-ITD AML. An extrapolation of the data suggests that patients aged 61–70 years with *FLT3*-ITD AML who are fit to receive 7+3 should be offered midostaurin since it seems to provide a survival benefit without undue toxicity. Schlenk RF, et al. Blood 2019;133:840-851.

[x] Regimens that include gemtuzumab ozogamicin have limited benefit in poor-risk disease.

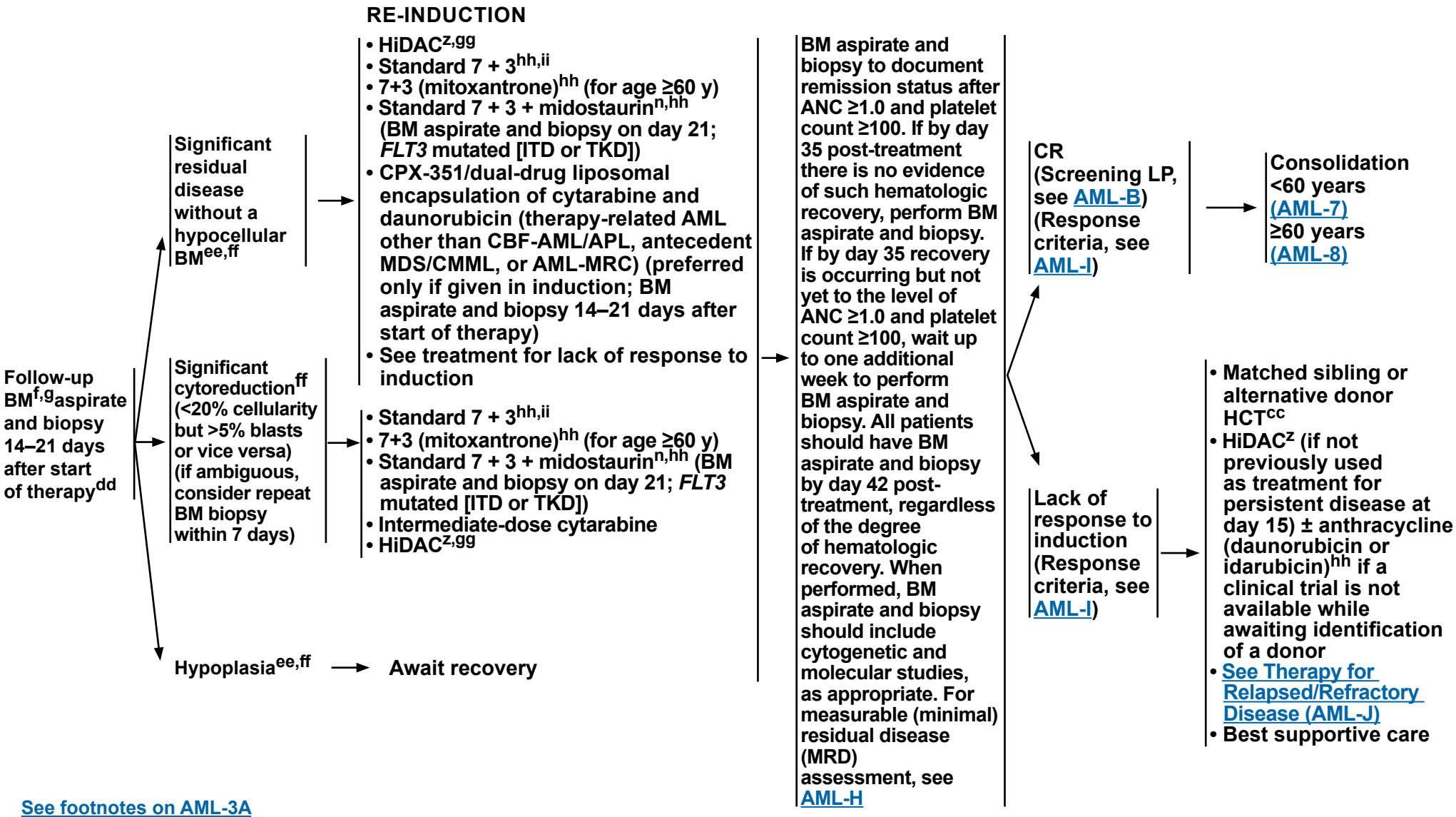
[y] In-frame bZIP mutations in *CEBPA* are more predictive of favorable outcomes than double mutations. Taube F, et al. Blood 2022;139:87-103; Wakita S, et al. Blood Adv 2022;6:238-247.

[z] Consider dose adjustments for cytarabine based on age and renal function.

[aa] The use of HiDAC for induction outside the setting of a clinical trial is still controversial. While the remission rates are the same for standard-dose cytarabine and HiDAC, two studies have shown more rapid BM blast clearance after one cycle of high-dose therapy. Kern W and Estey EH. Cancer 2006;107:116-124.

**Note: All recommendations are category 2A unless otherwise indicated.**
**Clinical Trials: NCCN believes that the best management of any patient with cancer is in a clinical trial. Participation in clinical trials is especially encouraged.**

## FOLLOW-UP AND REINDUCTION AFTER STANDARD-DOSE CYTARABINE INDUCTION[g,t,bb,cc]




See footnotes on AML-3A

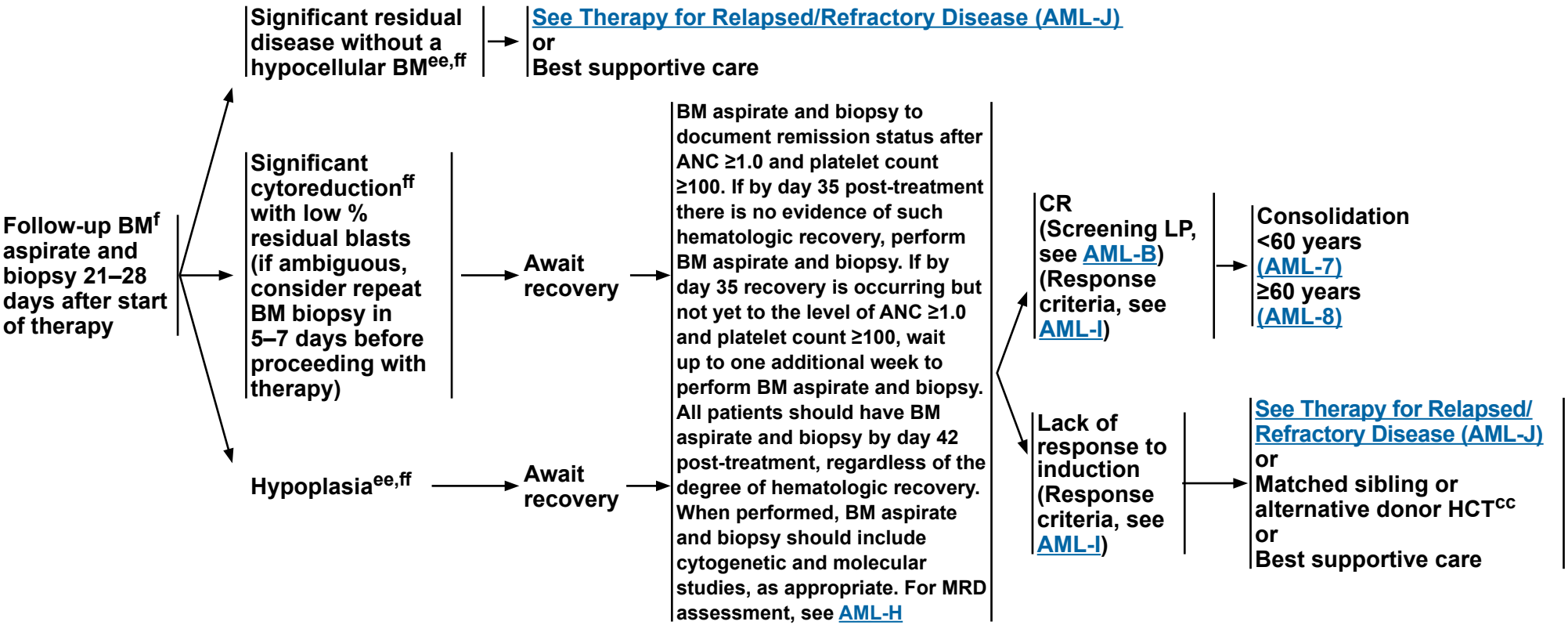
**Note: All recommendations are category 2A unless otherwise indicated.**
**Clinical Trials: NCCN believes that the best management of any patient with cancer is in a clinical trial. Participation in clinical trials is especially encouraged.**

## FOOTNOTES FOR FOLLOW-UP AND REINDUCTION AFTER STANDARD-DOSE CYTARABINE INDUCTION

[f] See Monitoring During Therapy (AML-G).
[g] Consider referral to palliative care for consultation at the start of induction. LeBlanc TW, et al. Curr Hematol Malig Rep 2017;12:300-308 and LeBlanc TW, et al. J Oncol Pract 2017;13:589-590. See NCCN Guidelines for Palliative Care.
[n] While midostaurin is not FDA approved for maintenance therapy, the study was designed for consolidation and maintenance midostaurin for a total of 12 months. Stone RM, et al. N Engl J Med 2017;377:454-464.
[t] See Principles of Systemic Therapy (AML-E).
[z] Consider dose adjustments for cytarabine based on age and renal function.
[bb] Consider clinical trials for patients with disease with targeted molecular abnormalities.
[cc] Begin alternate donor search (haploidentical, unrelated donor, or cord blood) if no appropriate matched sibling donor is available and the patient is a candidate for allogeneic HCT. For lack of response to induction, alternative therapy to achieve remission is encouraged prior to HCT. See NCCN Guidelines for Hematopoietic Cell Transplantation.
[dd] There are limited prospective data to support this recommendation. Othus M, et al. Leukemia 2016;30:1779-1780.
[ee] If ambiguous, consider repeat BM biopsy in 5–7 days before proceeding with therapy.
[ff] Hypoplasia is defined as cellularity less than 20% of which the residual blasts are less than 5% (ie, blast percentage of residual cellularity).
[gg] For re-induction, no data are available to show superiority with intermediate-dose cytarabine or HiDAC.
[hh] For regimens using high cumulative doses of cardiotoxic agents, consider reassessing cardiac function prior to each anthracycline/mitoxantrone-containing course. Karanes C, et al. Leuk Res 1999;23:787-794.
[ii] If daunorubicin 90 mg/m$^2$ was used in induction, the recommended dose for daunorubicin for reinduction prior to count recovery is 45 mg/m$^2$ for no more than 2 doses. Analogously, if idarubicin 12 mg/m$^2$ was used for induction, the early reinduction dose should be limited to 10 mg/m$^2$ for 1 or 2 doses.

**Note: All recommendations are category 2A unless otherwise indicated.**
**Clinical Trials: NCCN believes that the best management of any patient with cancer is in a clinical trial. Participation in clinical trials is especially encouraged.**

## FOLLOW-UP AFTER HIGH-DOSE CYTARABINE INDUCTION FOR POOR-RISK AML[g,bb,cc]




[f] See Monitoring During Therapy (AML-G).

[g] Consider referral to palliative care for consultation at the start of induction. LeBlanc TW, et al. Curr Hematol Malig Rep 2017;12:300-308 and LeBlanc TW, et al. J Oncol Pract 2017;13:589-590. See NCCN Guidelines for Palliative Care.

[bb] Consider clinical trials for patients with disease with targeted molecular abnormalities.

[cc] Begin alternate donor search (haploidentical, unrelated donor, or cord blood) if no appropriate matched sibling donor is available and the patient is a candidate for allogeneic HCT. For lack of response to induction, alternative therapy to achieve remission is encouraged prior to HCT. See NCCN Guidelines for Hematopoietic Cell Transplantation.

[ee] If ambiguous, consider repeat BM biopsy in 5–7 days before proceeding with therapy.

[ff] Hypoplasia is defined as cellularity less than 20% of which the residual blasts are less than 5% (ie, blast percentage of residual cellularity).

**Note: All recommendations are category 2A unless otherwise indicated.**
**Clinical Trials: NCCN believes that the best management of any patient with cancer is in a clinical trial. Participation in clinical trials is especially encouraged.**

**LOWER INTENSITY THERAPY (INTENSIVE INDUCTION INELIGIBLE)**

**Not a candidate for intensive induction therapy[a,b]**

**RISK GROUPS**

**AML without actionable mutations**

**TREATMENT INDUCTION[e,g,h,t]**
**Principles of Venetoclax, see AML-K**

**Preferred**
- Azacitidine + venetoclax (category 1)[q,r,oo]
- Decitabine (days 1–5) + venetoclax[q,r,oo]

**Other Recommended**
- LDAC + venetoclax[oo]
- Azacitidine or decitabine[r,jj]
- Glasdegib + LDAC[kk]
- Gemtuzumab ozogamicin[ll] (CD33 positive)[j] (category 2B)
- LDAC (category 2B)
- Best supportive care (hydroxyurea, transfusion support)

***IDH1* or *IDH2* mutation**

**Preferred**
- Azacitidine + venetoclax (category 1)[q,r,oo]
- Ivosidenib[mm,pp] + azacitidine[hn] (category 1) (*IDH1* only)
- Decitabine (days 1–5) + venetoclax[q,r,oo]
- Ivosidenib[mm,pp] (*IDH1* only)
- Enasidenib[mm,pp] (*IDH2* only)

**Other Recommended**
- LDAC + venetoclax[oo]
- Azacitidine, decitabine[r,jj]

**Useful in Certain Circumstances**
- Enasidenib[mm,pp] + azacitidine (*IDH2* only) (category 2B)

***FLT3* mutation**

**Preferred**
- Azacitidine + venetoclax (category 1)[q,r,oo]
- Decitabine (days 1–5) + venetoclax[q,r,oo]

**Other Recommended**
- LDAC + venetoclax[oo]
- Azacitidine or decitabine[r,jj] or sorafenib
- (Azacitidine or decitabine)[r] + sorafenib

**Useful in Certain Circumstances**
- Gilteritinib + azacitidine (category 2B)

Follow-Up After Induction Therapy With Lower Intensity Therapy (Intensive Induction Ineligible) (AML-6)

See footnotes on AML-5A

**Note: All recommendations are category 2A unless otherwise indicated.**
**Clinical Trials: NCCN believes that the best management of any patient with cancer is in a clinical trial. Participation in clinical trials is especially encouraged.**

## FOOTNOTES FOR LOWER INTENSITY THERAPY (INTENSIVE INDUCTION INELIGIBLE)

[a] Patients with elevated blast counts are at risk for tumor lysis and organ dysfunction secondary to leukostasis. Measures to rapidly reduce the WBC count include leukapheresis, hydroxyurea, and/or a single dose of cytarabine (1–2 g). Prompt institution of definitive therapy is essential.

[b] Poor performance/functional status and a comorbid medical condition, in addition to age, are factors that influence ability to tolerate standard induction therapy. Web-based tools available to evaluate the probability of CR and early death after standard induction therapy in patients aged ≥60 years with AML can be found at: Walter RB, et al. J Clin Oncol 2011;29:4417-4423; Borlenghi E, et al. J Geriatr Oncol 2021;12:550-556. See NCCN Guidelines for Older Adult Oncology.

[e] See Principles of Supportive Care for AML (AML-F).

[g] Consider referral to palliative care for consultation at the start of induction. LeBlanc TW, et al. Curr Hematol Malig Rep 2017;12:300-308 and LeBlanc TW, et al. J Oncol Pract.2017;13:589-590. See NCCN Guidelines for Palliative Care.

[h] See General Considerations and Supportive Care for Patients Who Prefer Not to Receive Blood Transfusions (AML-D).

[j] Threshold for CD33 is not well-defined and may be ≥1%.

[q] Venetoclax with decitabine, azacitidine, or LDAC may be continued for patients whose disease demonstrates clinical improvement (CR/CR with incomplete hematologic recovery [CRi]), with consideration of subsequent transplant, where appropriate. DiNardo CD, et al. Lancet Oncol 2018;19:216-228; Wei A, et al. Blood 2017;130:890; DiNardo CD, et al. Blood 2019;133:7-17; DiNardo CD, et al. N Engl J Med 2020;383:617-629.

[r] Patients whose disease has progressed to AML from MDS after significant exposure to HMAs (ie, azacitidine, decitabine) may be less likely to derive benefit from continued treatment with HMAs compared to patients who are HMA-naïve. Alternative treatment strategies should be considered. DiNardo CD, et al. Blood 2019;133:7-17.

[t] See Principles of Systemic Therapy.

[jj] In patients with AML with *TP53* mutation, a 10-day course of decitabine may be considered (Welch JS, et al. N Engl J Med 2016;375:2023-2036). Response may not be evident before 3–4 cycles of treatment with HMAs (ie, azacitidine, decitabine). Continue HMA treatment until progression if patient is tolerating therapy. Similar delays in response are likely with novel agents in a clinical trial, but endpoints will be defined by the protocol.

[kk] This regimen is for treatment of newly diagnosed AML in patients who are ≥75 years of age, or who have significant comorbid conditions (ie, severe cardiac disease, ECOG performance status ≥2, baseline creatinine >1.3 mg/dL) and has been associated with an improved OS in a randomized trial. Cortes JE, et al. Blood 2016;128:99.

[ll] Regimens that include gemtuzumab ozogamicin have limited benefit in poor-risk disease.

[mm] Enasidenib or ivosidenib increases the risk for differentiation syndrome and hyperleukocytosis that may require treatment with hydroxyurea and steroids. Monitor closely for differentiation syndrome and initiate therapy to resolve symptoms according to indications. Note that differentiation syndrome can occur later (up to several months after induction).

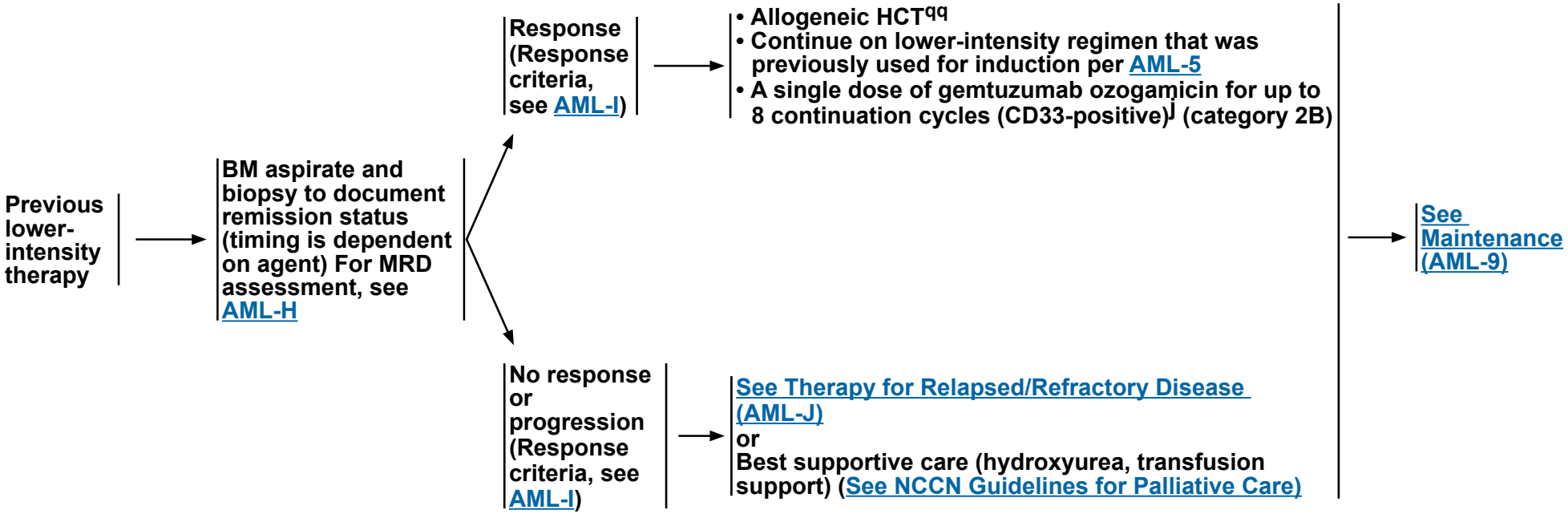
[nn] This regimen is approved for patients with newly diagnosed AML with an *IDH1* mutation who met at least one of the following criteria: aged >75 years, baseline ECOG performance status of 2, severe cardiac or pulmonary disease, hepatic impairment with bilirubin >1.5 times the upper limit of normal, creatinine clearance (CrCl) <45 mL/min, or other comorbidity. Montesinos P, et al. N Engl J Med 2022;386:1519-1531.

[oo] Patients with disease in remission should take breaks between cycles. For more details about cycle length, see AML-K.

[pp] Response to treatment with enasidenib or ivosidenib may take 3–5 months.

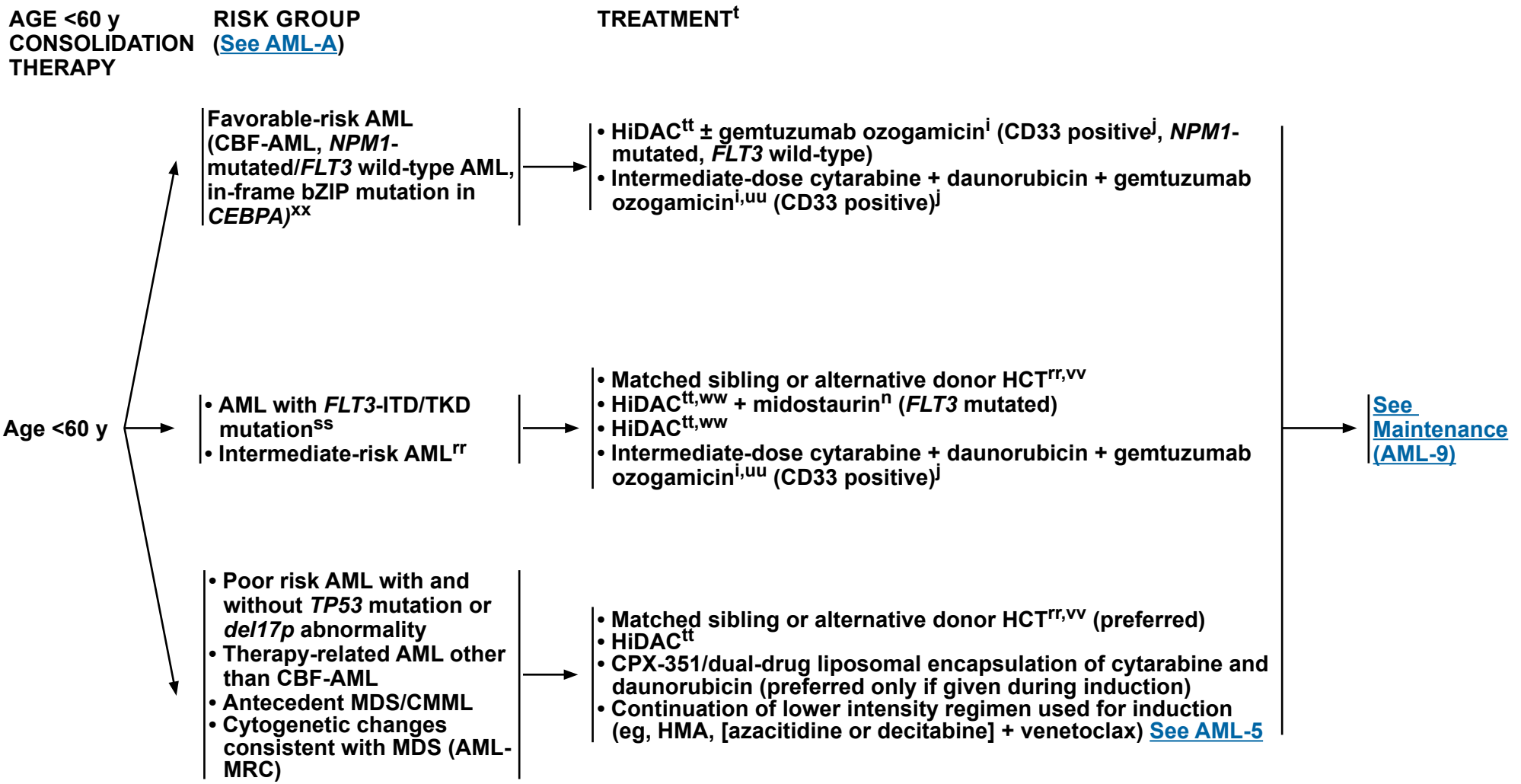
**Note: All recommendations are category 2A unless otherwise indicated.**
**Clinical Trials: NCCN believes that the best management of any patient with cancer is in a clinical trial. Participation in clinical trials is especially encouraged.**

## FOLLOW-UP AFTER INDUCTION THERAPY WITH LOWER INTENSITY THERAPY (INTENSIVE INDUCTION INELIGIBLE)[t]




[j] Threshold for CD33 is not well-defined and may be ≥1%.
[t] See Principles of Systemic Therapy.
[qq] Patients who are deemed as candidates for HCT and who have an available donor should be transplanted in first remission.

**Note: All recommendations are category 2A unless otherwise indicated.**
**Clinical Trials: NCCN believes that the best management of any patient with cancer is in a clinical trial. Participation in clinical trials is especially encouraged.**




See footnotes on AML-7A

**Note: All recommendations are category 2A unless otherwise indicated.**
**Clinical Trials: NCCN believes that the best management of any patient with cancer is in a clinical trial. Participation in clinical trials is especially encouraged.**

## FOOTNOTES FOR CONSOLIDATION THERAPY (AGE <60 YEARS)

[i] Patients who receive transplant shortly following gemtuzumab ozogamicin administration may be at risk for developing SOS. Wadleigh M, et al. Blood 2003;102:1578-1582. If transplant is planned, note that prior studies have used a 60- to 90-day interval between the last administration of gemtuzumab ozogamicin and HCT.

[j] Threshold for CD33 is not well-defined and may be ≥1%.

[n] While midostaurin is not FDA approved for maintenance therapy, the study was designed for consolidation and maintenance midostaurin for a total of 12 months. Stone RM, et al. N Engl J Med 2017;377:454-464.

[t] See Principles of Systemic Therapy.

[rr] Begin alternate donor search (haploidentical, unrelated donor, or cord blood) if no appropriate matched sibling donor is available and the patient is a candidate for allogeneic HCT. For lack of response to induction, alternative therapy to achieve remission is encouraged prior to HCT. See NCCN Guidelines for Hematopoietic Cell Transplantation.

[ss] *FLT3*-ITD mutation is a poor-risk feature in the setting of otherwise normal karyotype, and these patients should be considered for clinical trials where available.

[tt] Alternate dosing of cytarabine for postremission therapy has been reported (see Discussion). Jaramillo S, et al. Blood Cancer J 2017;7:e564.

[uu] This regimen may also be used in patients with AML with *KIT* mutations because the outcomes are similar in patients with AML without *KIT* mutations.

[vv] Patients may require at least one cycle of HiDAC consolidation while donor search is in progress to maintain remission. Patients may proceed directly to transplant following achievement of remission if a donor (sibling or alternative) is available.

[ww] There is no evidence that HiDAC is superior to intermediate doses (1.5 g/m$^2$ daily x 5 days) of cytarabine in patients with AML with intermediate-risk cytogenetics.

[xx] In-frame bZIP mutations in *CEBPA* are more predictive of favorable outcomes than double mutations. Taube F, et al. Blood 2022;139:87-103. Wakita S, et al. Blood Adv 2022;6:238-247.

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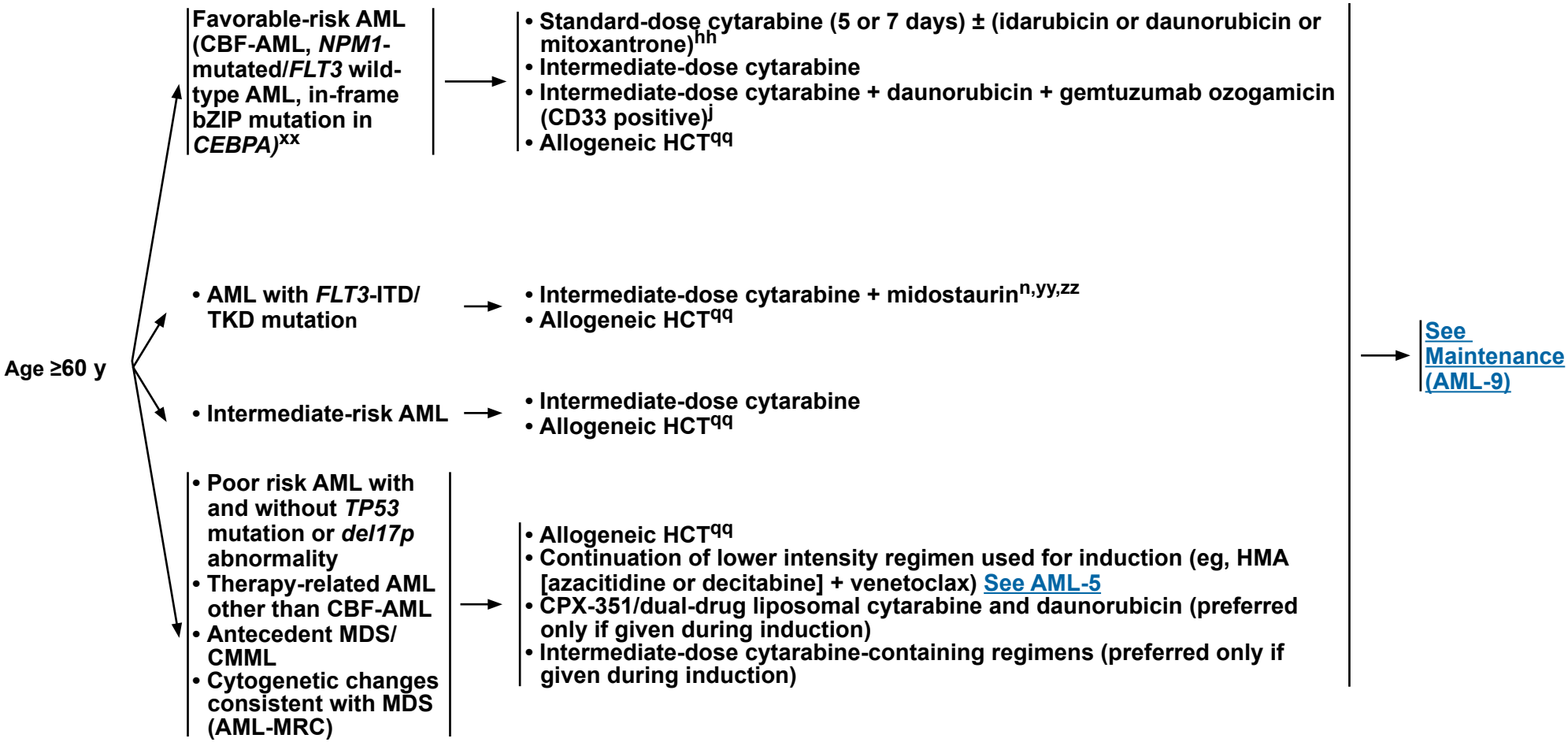
**Clinical Trials: NCCN believes that the best management of any patient with cancer is in a clinical trial. Participation in clinical trials is especially encouraged.**




See footnotes on AML-8A

**Note: All recommendations are category 2A unless otherwise indicated.**
**Clinical Trials: NCCN believes that the best management of any patient with cancer is in a clinical trial. Participation in clinical trials is especially encouraged.**

## FOOTNOTES FOR CONSOLIDATION THERAPY (AGE ≥60 YEARS)

[j] Threshold for CD33 is not well-defined and may be ≥1%.

[n] While midostaurin is not FDA approved for maintenance therapy, the study was designed for consolidation and maintenance midostaurin for a total of 12 months. Stone RM, et al. N Engl J Med 2017;377:454-464.

[t] See Principles of Systemic Therapy.

[hh] For regimens using high cumulative doses of cardiotoxic agents, consider reassessing cardiac function prior to each anthracycline/mitoxantrone-containing course. Karanes C, et al. Leuk Res 1999;23:787-794.

[qq] Patients who are deemed as candidates for HCT and who have an available donor should be transplanted in first remission.

[tt] Alternate dosing of cytarabine for postremission therapy has been reported (see Discussion). Jaramillo S, et al. Blood Cancer J 2017;7:e564.

[xx] In-frame bZIP mutations in *CEBPA* are more predictive of favorable outcomes than double mutations. Taube F, et al. Blood 2022;139:87-103. Wakita S, et al. Blood Adv 2022;6:238-247.

[yy] Alternate administration of intermediate-dose cytarabine may also be used. Sperr WG, et al. Clin Cancer Res 2004;10:3965-3971.

[zz] The RATIFY trial studied patients aged 18–60 y with *FLT3*-positive AML. An extrapolation of the data suggests that patients aged 61–70 years with *FLT3*-positive AML who are fit to receive 7+3 should be offered midostaurin since it seems to provide a survival benefit without undue toxicity. Schlenk RF, et al. Blood 2019;133:840-851.

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**Clinical Trials: NCCN believes that the best management of any patient with cancer is in a clinical trial. Participation in clinical trials is especially encouraged.**

| MAINTENANCE THERAPY | TREATMENT[t] |
|---|---|
| • Patient with intermediate or adverse risk disease:<br>▸ Who received prior intensive chemotherapy and whose disease is now in remission<br>▸ Completed no consolidation, some consolidation or a recommended course of consolidation and<br>▸ No allogeneic HCT is planned | • Maintenance therapy with oral azacitidine until progression or unacceptable toxicity (category 1, preferred for age ≥55 y)[zz]<br>• Maintenance therapy with HMA until progression or unacceptable toxicity<br>▸ Azacitidine<br>▸ Decitabine (category 2B) |
| Post allogeneic HCT, in remission, and history of *FLT3*-ITD | *FLT3* inhibitor maintenance<br>• Sorafenib<br>• Midostaurin (category 2B)<br>• Gilteritinib (category 2B) |
| Neither of the above scenarios is applicable | Maintenance therapy not recommended |

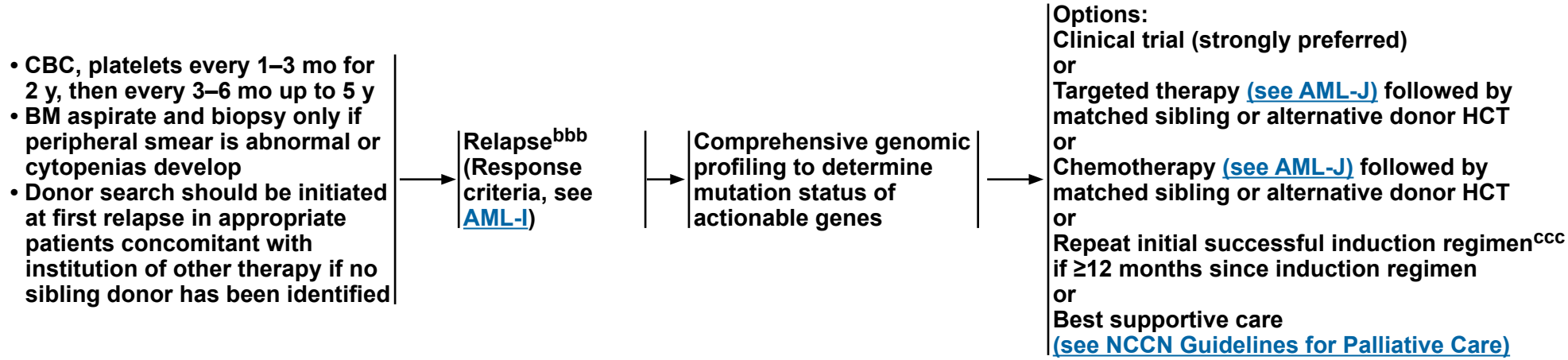
→ See Surveillance (AML-10)

[t] See Principles of Systemic Therapy.

[zz] This is not intended to replace consolidation chemotherapy. In addition, fit patients with AML with intermediate- and/or adverse-risk cytogenetics may benefit from HCT in first CR, and there are no data to suggest that maintenance therapy with oral azacitidine can replace HCT. The panel also notes that the trial did not include patients <55 years of age or those with CBF-AML; it was restricted to patients ≥55 years of age with AML with intermediate or adverse cytogenetics who were not felt to be candidates for HCT. Most patients received at least 1 cycle of consolidation prior to starting oral azacitidine. Wei AH, et al. N Engl J Med 2020;383:2526-2537.

**Note: All recommendations are category 2A unless otherwise indicated.**
**Clinical Trials: NCCN believes that the best management of any patient with cancer is in a clinical trial. Participation in clinical trials is especially encouraged.**

## AML SURVEILLANCE[aaa] AND THERAPY FOR RELAPSED/REFRACTORY DISEASE (AFTER COMPLETION OF CONSOLIDATION)




[aaa] Studies are ongoing to evaluate the role of molecular monitoring in the surveillance for early relapse in patients with AML (see Discussion).

[bbb] Multi-gene molecular profiling/targeted NGS (including *IDH1*/*IDH2*, *FLT3* mutations) is suggested as it may assist with selection of therapy and appropriate clinical trials (see Discussion). Molecular testing should be repeated at each relapse or progression.

[ccc] Reinduction therapy may be appropriate in certain circumstances, such as in patients with long first remission (there are no data regarding re-induction with dual-drug liposomal encapsulation of cytarabine and daunorubicin). This strategy primarily applies to cytotoxic chemotherapy and excludes the re-use of targeted agents due to the potential development of resistance. Targeted therapies may be retried if agents were not administered continuously and not stopped due to development of clinical resistance. If a second CR is achieved, then consolidation with allogeneic HCT should be considered.

**Note: All recommendations are category 2A unless otherwise indicated.**
**Clinical Trials: NCCN believes that the best management of any patient with cancer is in a clinical trial. Participation in clinical trials is especially encouraged.**

## RISK STRATIFICATION BY BIOLOGICAL DISEASE FACTORS FOR PATIENTS WITH NON-APL AML TREATED WITH INTENSIVE INDUCTION CHEMOTHERAPY[1,*]

| Risk Category[*,†] | Genetic Abnormality |
|---|---|
| Favorable | t(8;21)(q22;q22.1)/*RUNX1*::*RUNX1T1*[†,‡]<br>inv(16)(p13.1q22) or t(16;16)(p13.1;q22)/*CBFB*::*MYH11*[†,‡]<br>Mutated *NPM1*[†,§] without *FLT3*-ITD<br>bZIP in-frame mutated *CEBPA*[‖] |
| Intermediate | Mutated *NPM1*[†,§] with *FLT3*-ITD<br>Wild-type *NPM1* with *FLT3*-ITD (without adverse-risk genetic lesions)<br>t(9;11)(p21.3;q23.3)/*MLLT3*::*KMT2A*[†,¶]<br>Cytogenetic and/or molecular abnormalities not classified as favorable or adverse |
| Poor/Adverse | t(6;9)(p23.3;q34.1)/*DEK*::*NUP214*<br>t(v;11q23.3)/*KMT2A*-rearranged[#]<br>t(9;22)(q34.1;q11.2)/*BCR*::*ABL1*<br>t(8;16)(p11.2;p13.3)/*KAT6A*::*CREBBP*<br>inv(3)(q21.3q26.2) or t(3;3)(q21.3;q26.2)/*GATA2*, *MECOM(EVI1)*<br>t(3q26.2;v)/*MECOM(EVI1)*-rearranged<br>-5 or del(5q); -7; -17/abn(17p)<br>Complex karyotype,[**] monosomal karyotype[††]<br>Mutated *ASXL1*, *BCOR*, *EZH2*, *RUNX1*, *SF3B1*, *SRSF2*, *STAG2*, *U2AF1*, and/or *ZRSR2*[‡‡]<br>Mutated *TP53*[a] |

† Mainly based on results observed in intensively treated patients. Initial risk assignment may change during the treatment course based on the results from analyses of MRD.

‡ Concurrent *KIT* and/or *FLT3* gene mutation does not alter risk categorization

§ AML with *NPM1* mutation and adverse-risk cytogenetic abnormalities are categorized as adverse-risk.

‖ Only in-frame mutations affecting the bZIP region of *CEBPA*, irrespective of whether they occur as monoallelic or biallelic mutations, have been associated with favorable outcome.

¶ The presence of t(9;11)(p21.3;q23.3) takes precedence over rare, concurrent adverse-risk gene mutations.

# Excluding *KMT2A* partial tandem duplication (PTD).

** Complex karyotype: ≥3 unrelated chromosome abnormalities in the absence of other class-defining recurring genetic abnormalities; excludes hyperdiploid karyotypes with three or more trisomies (or polysomies) without structural abnormalities.

†† Monosomal karyotype: presence of two or more distinct monosomies (excluding loss of X or Y), or one single autosomal monosomy in combination with at least one structural chromosome abnormality (excluding CBF-AML).

‡‡ For the time being, these markers should not be used as an adverse prognostic marker if they co-occur with favorable-risk AML subtypes.

* Frequencies, response rates, and outcome measures should be reported by risk category, and, if sufficient numbers are available, by specific genetic lesions indicated.

a *TP53* mutation at a variant allele fraction of at least 10%, irrespective of the *TP53* allelic status (mono- or biallelic mutation); *TP53* mutations are significantly associated with AML with complex and monosomal karyotype.

1 Dohner H, Wei AH, Appelbaum FR, et al. Diagnosis and management of AML in adults: 2022 recommendations from an international expert panel on behalf of the ELN. Blood 2022;140:1345-1377.

For Familial Genetic Alterations in AML, see AML-A 2 of 4

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## FAMILIAL GENETIC ALTERATIONS IN AML[1]

- **Predisposition to AML is increasingly recognized. Referral for genetic counseling, germline tissue testing, and potential extension of these services to appropriate family members should be considered in select patients (See the NCCN Guidelines for Genetic/Familial High-Risk Assessment: Breast, Ovarian, and Pancreatic)**
- **With a suggestive family history of leukemia, other hematologic cancers, or the associated conditions listed in the tables on the next pages.**
  - **A diagnosis of MDS age <40 y or a personal history of ≥2 cancers (including those with therapy-related AML or MDS and at least one other cancer).**
  - **In whom a high variant allele frequency (>30%) mutation associated with AML predisposition was detected at diagnosis, particularly if it persists at high frequency in remission. These patients have a substantial risk of germline abnormalities and should be referred for assessment.**

- **An expeditious evaluation for germline AML predisposition mutations is of particular importance to assist family donor selection prior to allogeneic transplantation.**

- **Because commercial next-generation sequencing (NGS) panels for AML diagnostics sample neoplastic tissue and potentially lack coverage of genes or mutation hotspots, they should not be used in isolation to assess for the presence or absence of AML predisposition mutations. Germline mutation testing should only be performed on non-neoplastic tissues that do not carry a risk of blood contamination, such as cultured skin fibroblasts from a skin biopsy. This is not typically available outside of academic referral centers and has a prolonged turnaround time. Accordingly, it may be warranted to test the peripheral blood of family transplant donor candidates for suspect gene mutations identified in AML diagnosis or remission specimens before final results are available from germline tissue samples. Still, this testing should not replace referral for genetic counseling and germline assessment.**

[1] Kraft IL, Godley LA. Identifying potential germline variants from sequencing hematopoietic malignancies. Blood 2020;136:2498-2506.

Continued

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## FAMILIAL GENETIC ALTERATIONS IN AML

| Name of Syndrome | Causative Gene(s) | Pattern of Inheritance | Characteristic Malignancy | Other Hematopoietic Abnormalities | Other Associated Conditions | Recommended Diagnostic Test |
|---|---|---|---|---|---|---|
| Familial platelet disorder with propensity to myeloid malignancies (OMIM 601399) | *RUNX1* | Autosomal dominant | MDS<br>AML<br>T-cell ALL | Thrombocytopenia<br>Platelet dysfunction | | Exon sequencing and gene rearrangement testing for *RUNX1* |
| Thrombocytopenia 2 (OMIM 188000) | *ANKRD26* | Autosomal dominant | MDS<br>AML | Thrombocytopenia<br>Platelet dysfunction | | 5'UTR and exon sequencing of *ANKRD26* |
| Familial AML with mutated *CEBPA* (OMIM 116897) | *CEBPA* | Autosomal dominant | AML | | | Exon sequencing and gene rearrangement testing for *CEBPA* |
| Familial AML with mutated DDX41 (OMIM 608170) | *DDX41* | Autosomal dominant | MDS<br>AML<br>CMML | Monocytosis | Solid tumor predisposition is likely [colon, bladder, stomach, pancreas, breast, and melanoma] | Exon sequencing and gene rearrangement testing for *DDX41* |
| Thrombocytopenia 5 (OMIM 616216) | *ETV6* | Autosomal dominant | MDS<br>AML<br>CMML<br>B-ALL<br>Myeloma | Thrombocytopenia<br>Platelet dysfunction | | Exon sequencing and gene rearrangement testing for *ETV6* |
| Familial MDS/AML with mutated *GATA2* (OMIM 137295) | *GATA2* | Autosomal dominant | MDS<br>AML<br>CMML | Monocytopenia<br>Lymphopenia (NK cell, dendritic cell, B-cell, or CD4+ T-cell) | Sensorineural deafness<br>Immunodeficiency<br>Cutaneous warts<br>Pulmonary alveolar proteinosis<br>MonoMAC syndrome<br>Emberger syndrome | Exon sequencing, intron 5 enhancer region sequencing, and gene rearrangement testing for *GATA2* |

Continued

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## FAMILIAL GENETIC ALTERATIONS IN AML

| Name of Syndrome | Causative Gene(s) | Pattern of Inheritance | Characteristic Malignancy | Other Hematopoietic Abnormalities | Other Associated Conditions | Recommended Diagnostic Test |
|---|---|---|---|---|---|---|
| Familial AML with mutated *MBD4* | *MBD4* | Autosomal dominant | AML | | Colonic polyps | Exon sequencing and gene rearrangement testing for *MBD4* |
| *MECOM*-associated syndrome (OMIM 165215 and 616738) | *MECOM/EVI1* complex | Autosomal dominant | MDS<br>AML | Bone marrow failure<br>B-cell deficiency | Radioulnar synostosis<br>Clinodactyly<br>Cardiac malformations<br>Renal malformations<br>Hearing loss | Exon sequencing and gene rearrangement testing for *MECOM*/*EVI1* complex |
| Congenital *SAMD9/SAMD9L* mutations | *SAMD9* and *SAMD9L* | Autosomal dominant | MDS<br>AML | Pancytopenia | Normophosphatemic familial tumoral calcinosis<br>MIRAGE syndrome<br>Ataxia | Full gene sequencing and gene rearrangement testing for *SAMD9* and *SAMD9L* |
| Telomere syndromes due to mutation in *TERC* or *TERT* (OMIM 127550, 613989, and 615190) | *TERC,TERT and RTEL1* | Autosomal dominant<br><br>Autosomal recessive (*TERT*) | MDS<br>AML | Macrocytosis<br>Cytopenias<br>Aplastic anemia | Idiopathic pulmonary fibrosis<br>Hepatic cirrhosis<br>Nail dystrophy<br>Oral leukoplakia<br>Skin hypopigmentation<br>Skin hyperpigmentation<br>Premature gray hair<br>Cerebellar hypoplasia<br>Immunodeficiency<br>Developmental delay | Full gene sequencing and gene rearrangement testing for *TERT* and *TERC*<br><br>Telomere length studies of lymphocyte subsets via FlowFISH<br>SNP array testing (No CLIA-approved testing available) |
| Myeloid neoplasms with germline predisposition due to duplications of *ATG2B* and *GSKIP* | *ATG2B* and *GSKIP* | Autosomal dominant | AML<br>CMML<br>ET | Myelofibrosis | | SNP array testing (No CLIA-approved testing available) |

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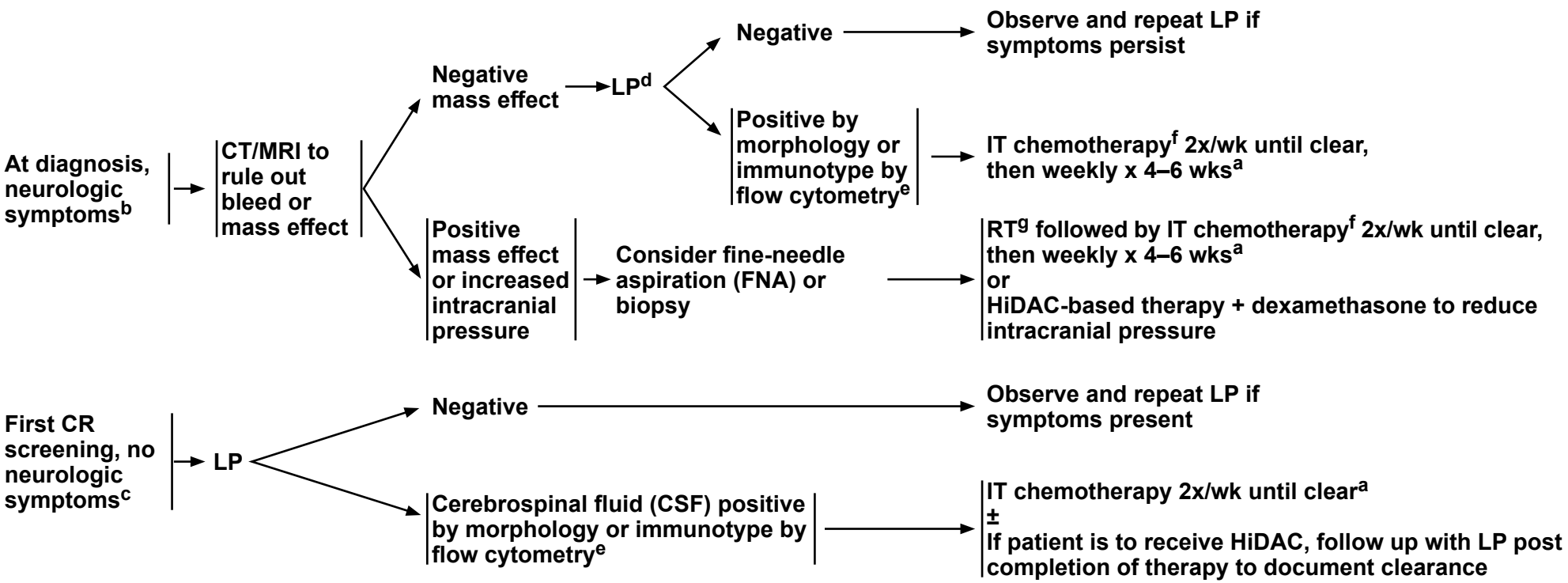
## EVALUATION AND TREATMENT OF CNS LEUKEMIA[a]




[a] Further CNS prophylaxis per institutional practice.
[b] For patients with major neurologic signs or symptoms at diagnosis, appropriate imaging studies should be performed to detect meningeal disease, chloromas, or CNS bleeding. LP should be performed if no mass, lesion, or hemorrhage was detected on the imaging study with central shift making an LP relatively contraindicated.
[c] Screening LP should be considered at first remission before first consolidation for patients with monocytic differentiation, MPAL, WBC count >40,000/mcL at diagnosis, extramedullary disease, high-risk APL, or *FLT3* mutations. For further information regarding MPAL, see NCCN Guidelines for Acute Lymphoblastic Leukemia.
[d] In the presence of circulating blasts, administer IT chemotherapy with diagnostic LP.
[e] If equivocal, consider repeating LP with morphology or immunotype by flow cytometry to delineate involvement.
[f] Induction chemotherapy should be started concurrently. However, for patients receiving HiDAC, since this agent crosses the blood brain barrier, IT therapy can be deferred until induction is completed. IT chemotherapy may consist of methotrexate, cytarabine, or a combination of these agents.
[g] Concurrent use of CNS RT with HiDAC or IT methotrexate may increase risk of neurotoxicity. See Principles of Radiation Therapy (AML-C).

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## PRINCIPLES OF RADIATION THERAPY

**General Principles**

- **Patients who present with isolated extramedullary disease (myeloid sarcoma) should be treated with systemic therapy. Local therapy (RT or surgery [rare cases]) may be used for residual disease.**
- **In a small group of patients where extramedullary disease is causing nerve compressions, a small dose of RT may be considered to decrease disease burden.**

**General Treatment Information**

- **Dosing prescription regimen**
  - **CNS leukemia: RT[a] followed by IT chemotherapy[b] 2x/wk until clear, then weekly x 4–6 weeks[c]**

[a] Concurrent use of CNS RT with HiDAC or IT methotrexate may increase risk of neurotoxicity.
[b] Induction chemotherapy should be started concurrently. However, for patients receiving HiDAC, since this agent crosses the blood-brain barrier, IT therapy can be deferred until induction is completed. IT chemotherapy may consist of methotrexate, cytarabine, or a combination of these agents.
[c] Further CNS prophylaxis per institutional practice.

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## GENERAL CONSIDERATIONS AND SUPPORTIVE CARE FOR PATIENTS WITH AML WHO PREFER NOT TO RECEIVE BLOOD TRANSFUSIONS[1-5]

### General Supportive Care

- There is no established treatment of AML that does not require the use of blood and blood products for supportive care.
- Discuss goals of care and understanding of complications without transfusion.
- For Jehovah's Witnesses, the United States Branch of the Christian Congregation of Jehovah's Witness has a Hospital Liaison Committee that can provide helpful information about bloodless medicine: https://www.jw.org/en/medical-library/hospital-liaison-committee-hlc-contacts/united-states
- Clarify acceptance of certain blood products (eg, cryoprecipitate) under certain circumstances, including a discussion of whether stem cells (donor or autologous) will be acceptable.
- Minimize blood loss (eg, use of pediatric collection tubes).
- Minimize risk of bleeding, including consideration for use of oral contraceptive pills or medroxyprogesterone acetate in menstruating individuals; proton pump inhibitor, aggressive antiemetic prophylaxis, and stool softeners to reduce risk of gastrointestinal (GI) bleed; nasal saline sprays to reduce epistaxis; and fall precautions particularly in patients with thrombocytopenia.
- Avoid concomitant medicines or procedures that can increase the risk of bleeding or myelosuppression.
- Consider using vitamin K (to potentially reverse coagulopathy) and aminocaproic acid or tranexamic acid in patients at risk of bleeding (eg, when platelet count drops below 30,000/μL) or for management of bleeding.
- Consider use of aminocaproic acid rinses for oral bleeding or significant mucositis that could result in bleeding.
- Consider using acetaminophen to manage fever.
- Consider iron, folate, and vitamin B12 supplementation if deficient. Iron supplementation may be avoided in someone with excess iron levels.
- Consider use of erythropoiesis-stimulation agent (ESA), G-CSF, and thrombopoietin (TPO) mimetics after a thorough discussion of potential risks, benefits, and uncertainties.
- Consider bed rest and supplemental oxygenation in patients with severe anemia.

### Disease-Specific Considerations

- Test for actionable mutations and consider use of targeted agents instead of intensive chemotherapy, particularly in a non-curative setting.
- May consider use of less myelosuppressive induction including dose reduction of anthracyclines, and use of non-intensive chemotherapy.[6]
- Consider referring to centers with experience in bloodless autologous HCT.

1 Laszio D, Agazzi A, Goldhirsch A, et al. Tailored therapy of adult acute leukaemia in Jehovah's Witnesses: unjustified reluctance to treat. Eur J Haematol 2004;72:264-267.
2 El Chaer F, Ballen KK. Treatment of acute leukaemia in adult Jehovah's Witnesses. Br J Haematol 2020;190:696-707.
3 Ballen KK, Becker PS, Yeap BY, et al. Autologous stem-cell cransplantation can be performed safely without the use of blood-product support. J Clin Oncol 2004;22:4087-4094.
4 Beck A, Lin R, Rejali AR, et al. Safety of bloodless autologous stem cell transplantation in Jehovah's Witness patients. Bone Marrow Transplant 2020;55:1059-1067.
5 Rubenstein M and Duvic M. Bone marrow transplantation in Jehovah's Witnesses. Leuk Lymphoma 2004;45:635-636.
6 Bock AM, Pollyea DA. Venetoclax with azacitidine for two younger Jehovah's Witness patients with high risk acute myeloid leukemia. Am J Hematol 2020;90:E269-E272

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## PRINCIPLES OF SYSTEMIC THERAPY
## INTENSIVE INDUCTION ELIGIBLE (AML-1, AML-2)

| Therapy | Regimen |
|---|---|
| Standard 7+3 (daunorubicin) + gemtuzumab ozogamicin[a,1,2] | Standard-dose cytarabine 200 mg/m$^2$ continuous infusion x 7 days with daunorubicin 60 mg/m$^2$ x 3 days and a single dose of gemtuzumab ozogamicin 3 mg/m$^2$ (up to one 4.5 mg vial) given on day 1, or day 2, or day 3, or day 4; alternatively, three total doses may be given on days 1, 4, and 7 |
| Standard 7+3 (daunorubicin or idarubicin) | Standard-dose cytarabine 100–200 mg/m$^2$ continuous infusion x 7 days with idarubicin 12 mg/m$^2$ or daunorubicin 60 or 90 mg/m$^2$ x 3 days |
| 7+3 (mitoxantrone)[b,c] | Standard-dose cytarabine 100-200 mg/m$^2$ continuous infusion x 7 days with mitoxantrone 12 mg/m$^2$ x 3 days |
| FLAG-IDA[d,1] | Fludarabine 30 mg/m$^2$ days 2–6, HiDAC 2 g/m$^2$ over 4 hours starting 4 hours after fludarabine infusion on days 2–6, idarubicin 8 mg/m$^2$ IV on days 4–6, and G-CSF subcutaneously (SC) daily days 1–7 |
| FLAG-IDA + gemtuzumab ozogamicin[a,d,3] | Fludarabine 30 mg/m$^2$ days 2–6, HiDAC 2 g/m$^2$ over 4 hours starting 4 hours after fludarabine infusion on days 2–6, idarubicin 8 mg/m$^2$ IV on days 4–6, and G-CSF SC daily days 1–7 plus a single dose of gemtuzumab ozogamicin 3 mg/m$^2$ in first course |
| Standard 7+3 (daunorubicin) + midostaurin | Standard-dose cytarabine 200 mg/m$^2$ continuous infusion x 7 days with daunorubicin 60 mg/m$^2$ x 3 days and oral midostaurin 50 mg every 12 hours, days 8–21 |
| FLAG-IDA[3] + venetoclax[4] | Fludarabine 30 mg/m$^2$ days 2–6, HiDAC[c] 1.5 g/m$^2$ over 4 hours starting 4 hours after fludarabine infusion on days 2–6, idarubicin 8 mg/m$^2$ IV on days 4–6, and G-CSF SC daily days 1–7 plus venetoclax 400 mg PO days 1–14 |

[a] A meta-analysis showing an advantage with gemtuzumab ozogamicin included other dosing schedules. Hills RK, et al. Lancet Oncol 2014; 15:986-996
[b] For age ≥60 years
[c] For regimens using high cumulative doses of cardiotoxic agents, consider reassessing cardiac function prior to each anthracycline/mitoxantrone-containing course. Karanes C, et al. Leuk Res 1999;23:787-794.
[d] Use with caution in patients >60 years.

[1] Burnett AK, et al. J Clin Oncol 2011;29:369-377.
[2] Castaigne S et al. Lancet 2012;379:1508-1516.
[3] Burnett AK, et al. J Clin Oncol 2013;31:3360-3368.
[4] DiNardo CD, et al. Am J Hematol 2022;97:1035-1043.

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## PRINCIPLES OF SYSTEMIC THERAPY
## INTENSIVE INDUCTION ELIGIBLE (AML-1, AML-2)

| Therapy | Regimen |
|---|---|
| HiDAC + (daunorubicin or idarubicin) + etoposide[5-7] | HiDAC 2 g/m$^2$ every 12 hours x 6 days or 3 g/m$^2$ every 12 hours x 4 days with daunorubicin 50 mg/m$^2$ or idarubicin 12 mg/m$^2$ x 3 days, and etoposide 50 mg/m$^2$ days 1 to 5 (1 cycle) |
| Decitabine (days 1-5) + venetoclax | Decitabine 20 mg/m$^2$ IV (days 1–5 of each 28-day cycle) and venetoclax PO once daily (100 mg day 1, 200 mg day 2, and 400 mg day 3 and beyond) |
| Decitabine (days 1-10) + venetoclax | Decitabine 20 mg/m$^2$ IV (days 1–10 of each 28-day cycle) and venetoclax PO once daily (100 mg day 1, 200 mg day 2, and 400 mg day 3 and beyond) |
| Azacitidine + venetoclax | Azacitidine 75 mg/m$^2$ SC or IV days 1–7 of each 28-day cycle and venetoclax PO once daily (100 mg day 1, 200 mg day 2, and 400 mg days 3 and beyond) |
| LDAC + venetoclax[8] | LDAC 20 mg/m$^2$/d SC days 1–10 of each 28-day cycle and venetoclax PO once daily (100 mg day 1, 200 mg day 2, 400 mg day 3, and 600 mg days 4 and beyond) |
| Low-intensity therapy (azacitidine or decitabine) | Azacitidine 75 mg/m$^2$ SC or IV days 1–7 of each 28-day cycle<br>Decitabine 20 mg/m$^2$/day IV (days 1–5 or days 1–10 of each 28-day cycle) |
| CPX-351/dual-drug liposomal cytarabine and daunorubicin[9] | CPX-351/dual-drug liposomal cytarabine 100 mg/m$^2$ and daunorubicin 44 mg/m$^2$ on days 1, 3, and 5 x 1 cycle |

5 Weick JKK, et al. Blood 1996; 88:2841-2851.
6 Bishop JF et al. Blood 1996;87:1710-1717.
7 Willemze R et al. J Clin Oncol 2014;32:219-228.
8 Wei AH, et al. J Clin Oncol 2019;27:1277-1284.
9 Lancet JE, et al. J Clin Oncol 2018;36:2684-2692.

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## PRINCIPLES OF SYSTEMIC THERAPY
## FOLLOW-UP AND REINDUCTION AFTER STANDARD-DOSE CYTARABINE INDUCTION (AML-3)

| Therapy | Regimen |
|---|---|
| HiDAC | Cytarabine 1.5–3 g/m$^2$ over 3 hours every 12 hours on days 1, 3, and 5, or days 1, 2, and 3 for 3–4 cycles |
| Standard 7+3 (daunorubicin or idarubicin) | Standard-dose cytarabine 100–200 mg/m$^2$ continuous infusion x 7 days with daunorubicin 60–90 mg/m$^2$ or idarubicin 12 mg/m$^2$ x 3 days |
| Standard 7+3 (daunorubicin) + midostaurin | Standard-dose cytarabine 200 mg/m$^2$ continuous infusion x 7 days with daunorubicin 60 mg/m$^2$ x 3 days and oral midostaurin 50 mg every 12 hours, days 8–21 |
| CPX-351/dual-drug liposomal cytarabine and daunorubicin[9] | CPX-351/dual-drug liposomal cytarabine 100 mg/m$^2$ and daunorubicin 44 mg/m$^2$ on days 1, 3, and 5 x 1 cycle |
| Intermediate-dose cytarabine | Cytarabine 1 – 1.5 g/m$^2$ over 3 hours every 12 hours x 4–6 doses for 1–2 cycles |
| HiDAC ± (daunorubicin or idarubicin) | HiDAC 2 g/m$^2$ every 12 hours x 6 days or 3 g/m$^2$ every 12 hours x 4 days with daunorubicin 50 mg/m$^2$ or idarubicin 12 mg/m$^2$ x 3 days |

[9] Lancet JE, et al. J Clin Oncol 2018;36:2684-2692.

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## PRINCIPLES OF SYSTEMIC THERAPY
## LOWER INTENSITY THERAPY (INTENSIVE INDUCTION INELIGIBLE) AML WITHOUT ACTIONABLE MUTATIONS (AML-5)

| Therapy | Regimen |
|---|---|
| Azacitidine + venetoclax[10] | Azacitidine 75 mg/m$^2$ SC or IV days 1–7 of each 28-day cycle and venetoclax PO once daily (100 mg day 1, 200 mg day 2, and 400 mg days 3 and beyond) |
| Decitabine + venetoclax | Decitabine 20 mg/m$^2$ IV (days 1–5) and venetoclax PO once daily (100 mg day 1, 200 mg day 2, and 400 mg day 3 and beyond) |
| LDAC + venetoclax[11] | LDAC 20 mg/m$^2$/day SC days 1–10 of each 28-day cycle and venetoclax PO once daily (100 mg day 1, 200 mg day 2, 400 mg day 3 and 600 mg days 4 and beyond) |
| Azacitidine | 75 mg/m$^2$ SC or IV days 1–7 of each 28-day cycle |
| Decitabine | 20 mg/m$^2$/day IV (days 1–5 of each 28-day cycle) |
| Glasdegib + LDAC[e] | Glasdegib (100 mg PO daily on days 1–28) + LDAC 20 mg SC every 12 hours (days 1–10 of each 28-day cycle) |
| Gemtuzumab ozogamicin[a,1,12] | 6 mg/m$^2$ IV on day 1 and 3 mg/m$^2$ IV on day 8 |
| LDAC[11] | 20 mg/m$^2$/day SC (days 1–10 of each 28-day cycle) |
| Hydroxyurea (best supportive care) | Adjust dose based on WBC count and tolerance |

[a] A meta-analysis showing an advantage with gemtuzumab ozogamicin included other dosing schedules. Hills RK, et al. Lancet Oncol 2014; 15:986-996

[e] This regimen is for treatment of newly diagnosed AML in patients who are ≥75 years of age, or who have significant comorbid conditions (ie, severe cardiac disease, ECOG performance status ≥2, baseline creatinine >1.3 mg/dL) and has been associated with an improved OS in a randomized trial. Cortes JE, et al. Blood 2016;128:99.

[1] Burnett AK, et al. J Clin Oncol 2011;29:369-377.
[10] DiNardo CD, et al. N Engl J Med 2020;383:617-629.
[11] Kantarjian HM, et al. J Clin Oncol 2012;30:2670-2677.
[12] Amadori S, et al. J Clin Oncol 2016;34:972-979.

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## PRINCIPLES OF SYSTEMIC THERAPY
## LOWER INTENSITY THERAPY (INTENSIVE INDUCTION INELIGIBLE) *IDH1* OR *IDH2* MUTATION (AML-5)

| Therapy | Regimen |
|---|---|
| Ivosidenib[13] | 500 mg PO once daily on days 1–28 of a 28-day cycle |
| Ivosidenib + azacitidine | Ivosidenib 500 mg PO once daily on days 1–28 and azacitidine 75 mg/m$^2$ SC or IV (days 1–7 or days 1–5, 8, and 9 of each 28-day cycle) |
| Enasidenib[14] | 100 mg PO once daily on days 1–28 of a 28-day cycle |
| Enasidenib + azacitidine | Enasidenib 100 mg daily on days 1-28 and azacitidine 75 mg/m$^2$ SC or IV on days 1-7 of each 28 day cycle |

[13] DiNardo CD, et al. Blood 2017;130:725; DiNardo CD, et al. Blood 2017;130:639; Roboz GJ, et al. Blood 2020;135:462-471.
[14] Stein EM, et al. Blood 2015;126:323; DiNardo CD, et al. Blood 2017;130:639.

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## PRINCIPLES OF SYSTEMIC THERAPY
## LOWER INTENSITY THERAPY (INTENSIVE INDUCTION INELIGIBLE) *FLT3* MUTATION (AML-5)

| Therapy | Regimen |
|---|---|
| Sorafenib | 400 mg PO twice daily days 1–28 of each 28-day cycle |
| (Azacitidine or decitabine) + sorafenib[15] | Azacitidine 75 mg/m$^2$ SC or IV days 1–7 of each 28-day cycle or<br>Decitabine 20 mg/m$^2$ IV days 1–10 of each 28-day cycle + sorafenib 400 mg PO twice daily days 1–28 of each 28-day cycle |
| Gilteritinib + azacitidine | Gilteritinib 120 mg daily on days 1-28 and azacitidine 75 mg/m$^2$ SC or IV on days 1-7 of each 28 day cycle |

[15] Ohanian M, et al. Am J Hematol 2018;93;1136-1141.

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## PRINCIPLES OF SYSTEMIC THERAPY
## FOLLOW-UP AFTER INDUCTION THERAPY WITH LOWER INTENSITY THERAPY (INTENSIVE INDUCTION INELIGIBLE)
## (AML-6)

| Therapy | Regimen |
|---|---|
| Gemtuzumab ozogamicin[a,1,12] | 6 mg/m$^2$ IV on day 1 and 3 mg/m$^2$ IV on day 8 |
| See AML-5 for other regimens | |
| See AML-7 or AML-8 for consolidation | |

## CONSOLIDATION AGE <60 YEARS
## (AML-7)

| Therapy | Regimen |
|---|---|
| HiDAC[16,17] + gemtuzumab ozogamicin[a,1] | Cytarabine 3 g/m$^2$ over 3 hours every 12 hours on days 1, 3, and 5 or on days 1, 2, and 3 x 3–4 cycles with gemtuzumab ozogamicin 3 mg/m$^2$ (maximum dose 4.5 mg) on day 1 x 2 cycles |
| Intermediate-dose cytarabine + daunorubicin + gemtuzumab ozogamicin[a,1] | Cytarabine 1-1.5 g/m$^2$ every 12 hours on days 1–4 + daunorubicin 60 mg/m$^2$ on day 1 (first cycle) or days 1–2 (second cycle) + gemtuzumab ozogamicin 3 mg/m$^2$ (maximum dose 4.5 mg) on day 1 x 2 cycles |
| HiDAC[16,17] + midostaurin | Cytarabine 1.5–3 g/m$^2$ over 3 hours every 12 hours on days 1, 3, and 5 or days 1, 2, and 3 x 3–4 cycles + midostaurin 50 mg twice daily on days 8–21 x 4 cycles |
| HiDAC[16,17] | Cytarabine 1.5–3 g/m$^2$ over 3 hours every 12 hours on days 1, 3, and 5 or days 1, 2, and 3 x 3–4 cycles |
| CPX-351/dual-drug liposomal cytarabine and daunorubicin[9] | CPX-351/dual-drug liposomal cytarabine 65 mg/m$^2$ and daunorubicin 29 mg/m$^2$ on day 1 and 3 x 1 – 2 cycles |

[1] Burnett AK, et al. J Clin Oncol 2011;29:369-377.
[9] Lancet JE, et al. J Clin Oncol 2018; 36:2684-2692.
[12] Amadori S, et al. J Clin Oncol 2016;34:972-979.
[16] Mayer RJ, et al. N Engl J Med 1994;331:896-903
[17] Jaramillo S, et al. Blood Cancer J 2017;7: e564

[a] A meta-analysis showing an advantage with gemtuzumab ozogamicin included other dosing schedules. Hills RK, et al. Lancet Oncol 2014;15:986-996.

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## PRINCIPLES OF SYSTEMIC THERAPY
## CONSOLIDATION AGE ≥60 YEARS
## (AML-8)

| Therapy | Regimen |
|---|---|
| Standard-dose cytarabine (5 or 7 days) ± (idarubicin or daunorubicin or mitoxantrone)[c] | Cytarabine (100–200 mg/m$^2$ over 5–7 days x 1–2 cycles) +/- idarubicin 10 mg/m$^2$ or daunorubicin 45 mg/m$^2$ or mitoxantrone 12 mg/m$^2$ x 3 days |
| Intermediate-dose cytarabine | Cytarabine 1–1.5 g/m$^2$ x 4–6 doses for 1–2 cycles |
| Intermediate-dose cytarabine + daunorubicin + gemtuzumab ozogamicin[a,1] | Cytarabine 1–1.5 g/m$^2$ x 4–6 doses for 1–2 cycles + daunorubicin 60 mg/m$^2$ on day 1 (first cycle) or days 1–2 (second cycle) + gemtuzumab ozogamicin 3 mg/m$^2$ (maximum dose 4.5 mg) on day 1 x 2 cycles |
| Intermediate-dose cytarabine + midostaurin | Cytarabine 1–1.5 g/m$^2$ over 3 hours every 12 hours on days 1, 3, and 5 or days 1, 2, and 3 x 3–4 cycles + midostaurin 50 mg twice daily on days 8–21 x 4 cycles |
| CPX-351/dual-drug liposomal cytarabine and daunorubicin[9] | CPX-351/dual-drug liposomal cytarabine 65 mg/m$^2$ and daunorubicin 29 mg/m$^2$ on day 1 and 3 x 1–2 cycles |
| See AML-5 for continuation of of lower intensity therapy | |

[a] A meta-analysis showing an advantage with gemtuzumab ozogamicin included other dosing schedules. Hills RK, et al. Lancet Oncol 2014;15:986-996.

[c] For regimens using high cumulative doses of cardiotoxic agents, consider reassessing cardiac function prior to each anthracycline/mitoxantrone-containing course. Karanes C, et al. Leuk Res 1999;23:787-794.

[1] Burnett AK, et al. J Clin Oncol 2011;29:369-377.
[9] Lancet JE, et al. J Clin Oncol 2018; 36:2684-2692.

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## PRINCIPLES OF SYSTEMIC THERAPY
## MAINTENANCE THERAPY
## (AML-9)

| Therapy | Regimen |
|---|---|
| Oral azacitidine | 300 mg PO daily on days 1–14 of each 28-day cycle |
| Azacitidine[18] | 75 mg/m$^2$ IV daily on days 1–7 or days 1–5, 8, and 9 of a 28-day cycle |
| Decitabine[19] | 20 mg/m$^2$ IV daily on days 1–5 of a 28-day cycle |
| Sorafenib[20,21] | 200 mg PO twice daily on days 1–28 x 3 cycles, then 400 mg PO twice daily on days 1–28 (based on tolerance, continue until 24 months of therapy have been completed) |
| Midostaurin | 50 mg PO twice daily on days 1–28 of each 28-day cycle x 12 cycles |
| Gilteritinib[22] | 120 mg PO daily, days 1–28 of each 28-day cycle (up to 26 cycles) |

[18] Huls G, et al. Blood 2019;133:1457-1464.
[19] Boumber Y, et al. Leukemia 2012;26:2428-3241.
[20] Xuan L, et al. Lancet Oncol 2020;21:1201-1212.
[21] Burchert A, et al. J Clin Oncol 2020;38:2993-3002.
[22] Pratz KW, et al. Blood 2020;136 (supplement 1):16-17.

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## PRINCIPLES OF SUPPORTIVE CARE FOR AML

**There are variations among institutions, but the following issues are important to consider in the management of AML.**

**General**

- **Blood products:**
  - **Leukocyte-depleted products should be used for transfusion.**
  - **All patients with AML are at risk for acute graft-versus-host disease (aGVHD) and management should be based on institutional practice/ preference. See NCCN Guidelines for Hematopoietic Cell Transplantation.**
  - **Transfusion thresholds: red blood cell (RBC) counts for hemoglobin ≤7–8 g/dL or per institutional guidelines or symptoms of anemia; platelets for patients with platelets <10,000/mcL or with any signs of bleeding.[a]**
  - **Cytomegalovirus (CMV) screening for potential HCT candidates may be considered.**
- **Tumor lysis prophylaxis: hydration with diuresis, and allopurinol or rasburicase. Rasburicase should be considered as initial treatment in patients with rapidly increasing blast counts, high uric acid, or evidence of impaired renal function.**
  - **Glucose-6-phosphate dehydrogenase (G6PD) deficiency should be checked when possible. However, it is not always feasible to do so rapidly. If there is high suspicion of G6PD deficiency, caution is necessary; rasburicase may be contraindicated.**
- **Patients receiving HiDAC therapy (particularly those with impaired renal function), or intermediate-dose cytarabine in patients >60 years of age, are at risk for cerebellar toxicity. Neurologic assessment, including tests for nystagmus, slurred speech, and dysmetria, should be performed before each dose of cytarabine.**
  - **In patients exhibiting rapidly rising creatinine due to tumor lysis, HiDAC should be discontinued until creatinine normalizes.**
  - **In patients who develop cerebellar toxicity, cytarabine should be stopped. Rechallenge with HiDAC in future treatment cycles should not be attempted.[1]**
- **Steroid (or equivalent) eye drops should be administered to both eyes 4 times daily for all patients undergoing HiDAC therapy until 24 hours post completion of cytarabine.**
- **Growth factors may be considered as a part of supportive care for post-remission therapy. Note that such use may confound interpretation of the BM evaluation. Patients should be off granulocyte-macrophage colony-stimulating factor (GM-CSF) or G-CSF for a minimum of 7 days before obtaining BM to document remission.**
- **Decisions regarding use and choice of antibiotics should be made by the individual institutions based on the prevailing organisms and their drug resistance patterns. Posaconazole has been shown to significantly decrease fungal infections when compared to fluconazole and itraconazole.[2] Outcomes with other azoles, such as voriconazole, echinocandins, or amphotericin B, may produce equivalent results. See the NCCN Guidelines for the Prevention and Treatment of Cancer-Related Infections and commensurate with the institutional practice for antibiotic stewardship.**

[a] Patients who are alloimmunized should receive cross-match–compatible and/or HLA-specific blood products

[1] Smith GA, Damon LE, Rugo HS, et al. High-dose cytarabine dose modification reduces the incidence of neurotoxicity in patients with renal insufficiency. J Clin Oncol 1997;15:833-839.

[2] Cornely OA, Maertens J, Winston DJ, et al. Posaconazole vs. fluconazole or itraconazole prophylaxis in patients with neutropenia. N Engl J Med 2007;356:348-359.

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## MONITORING DURING THERAPY

**Induction**

- CBC daily (differential daily or as clinically indicated during chemotherapy and every other day after recovery of WBC count >500/mcL until either normal differential or persistent leukemia is documented); platelets daily while in the hospital until platelet-transfusion independent.
- Chemistry profile, including electrolytes, liver function tests (LFTs), blood urea nitrogen (BUN), creatinine, uric acid, and phosphorous, at least daily during active treatment until risk of tumor lysis is past. If the patient is receiving nephrotoxic agents, closer monitoring is required through the period of hospitalization.
- LFTs 1–2 x/wk.
- Coagulation panel 1–2 x/wk.
  - For patients who have evidence of disseminated intravascular coagulation (DIC), coagulation parameters including fibrinogen should be monitored daily until resolution of DIC.
- BM aspirate/biopsy 14–21 days after start of therapy to document hypoplasia. If hypoplasia is not documented or indeterminate, repeat biopsy in 7–14 days to clarify persistence of leukemia. If hypoplasia, then repeat biopsy at time of hematologic recovery to document remission. If cytogenetics were initially abnormal, include cytogenetics as part of the remission documentation.

**Post-Remission Therapy**

- CBC, platelets 2x/wk during chemotherapy.
- Chemistry profile, electrolytes daily during chemotherapy.
- Outpatient monitoring post chemotherapy: CBC, platelets, differential, and electrolytes 2–3 x/wk until recovery.
- BM aspirate/biopsy only if peripheral blood counts are abnormal or if counts have not recovered within 5 weeks.
- Patients with AML with high-risk features, including poor-prognosis cytogenetics, therapy-related AML, prior MDS, or possibly 2 or more inductions to achieve a CR are at increased risk for relapse and should be considered for early alternate donor search, as indicated on AML-7.

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## MEASURABLE (MINIMAL) RESIDUAL DISEASE ASSESSMENT

- **The role of MRD in prognosis and treatment is evolving. Participation in clinical trials is encouraged.**
- **MRD in AML refers to the presence of leukemic cells below the threshold of detection by conventional morphologic methods. MRD is a component of disease evaluation over the course of sequential therapy. If the patient is not treated in an academic center, there are commercially available tests available that can be used for MRD assessment. Patients whose disease achieved a CR by morphologic assessment alone can still harbor a large number of leukemic cells in the BM.[1] The points discussed below are relevant to intensive approaches (induction chemotherapy) but have not been validated for other modalities of treatment.**
- **The most frequently employed methods for MRD assessment include real-time quantitative PCR (RQ-PCR) assays (ie, *NPM1*,[2] CBFB*::MYH11*, *RUNX1::RUNX1T1*[3]) and multicolor flow cytometry (MFC) assays specifically designed to detect abnormal MRD immunophenotypes.[1] The threshold to define MRD+ and MRD- samples depends on the technique and subgroup of AML. NGS–based assays to detect mutated genes (targeted sequencing, 20–50 genes per panel)[4,5] is not routinely used, as the sensitivity of PCR-based assays and flow cytometry is superior to what is achieved by conventional NGS. Mutations associated with clonal hematopoiesis of indeterminate potential (CHIP) and aging (ie, *DNMT3A*, *TET2*, potentially *ASXL1*) are also not considered reliable markers for MRD.[4-6]**
  - **There are distinct differences between diagnostic threshold assessments and MRD assessments. If using flow cytometry to assess MRD, it is recommended that a specific MRD assay is utilized, but, most importantly, that it is interpreted by an experienced hematopathologist.**
- **Based on the techniques, the optimal sample for MRD assessment is either peripheral blood (*NPM1* PCR-based techniques) or an early, dedicated pull of the BM aspirate (ie, other PCR, flow cytometry, NGS). The quality of the sample is of paramount importance to have reliable evaluation.**
- **Studies in both children and adults with AML have demonstrated the correlation between MRD and risks for relapse, as well as the prognostic significance of MRD measurements after initial induction therapy.[7]**
  - **MRD positivity is not proof of relapse. However, a persistently positive MRD result after induction, which depends on the technique used and the study, is associated with an increased risk of relapse.**
  - **Forpatients with favorable-risk disease, if MRD is persistently positive after induction and/or consolidation, consider a clinical trial or alternative therapies, including allogeneic HCT.**
  - **Some evidence suggests MRD testing may be more prognostic than *KIT* mutation status in CBF-AML, but this determination depends on the method used to assess MRD and the trend of detectable MRD.**
  - **After completion of therapy, "Molecular relapses" can predict hematologic relapses within a 3- to 6-month timeframe.**
- **Timing of MRD assessment:**
  - **Upon completion of initial induction.[4-6]**
  - **Before allogeneic HCT.[8]**
  - **Additional time points should be guided by the regimen used.[2,3]**

1 Schuurhuis GJ, Heuser M, Freeman S, et al. Minimal/measurable residual disease in AML: consensus document from ELN MRD Working Party. Blood 2018;131:1275-1291.
2 Ivey A, Hills RK, Simpson MA, et al. Assessment of minimal residual disease in standard-risk AML. N Engl J Med 2016;374:422-433.
3 Jourdan E, Boissel N, Chevret S, et al. Prospective evaluation of gene mutations and minimal residual disease in patients with core binding factor acute myeloid leukemia. Blood 2013;121:2213-2223.
4 Jongen-Lavrencic M, Grob T, Hanekamp D, et al. Molecular minimal residual disease in acute myeloid leukemia. N Engl J Med 2018;378:1189-1199.
5 Klco JM, Miller CA, Griffith M, et al. Association between mutation clearance after induction therapy and outcomes in acute myeloid leukemia. JAMA 2015;314:811-822.
6 Morita K, Kantarjian H, Wang F, et al. Clearance of somatic mutations at remission and the risk of relapse in acute myeloid leukemia J Clin Oncol 2018 36:1788-1797.
7 Short NJ, et al. Association of measurable residual disease with survival outcomes in patients with acute myeloid leukemia: A systematic review and meta-analysis. JAMA Oncol 2020;6:1890-1899.
8 Thol F, Gabdoulline R, Liebich A, et al. Measurable residual disease monitoring by NGS before allogeneic hematopoietic cell transplantation in AML. Blood 2018;132:1703-1713.

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## RESPONSE CRITERIA DEFINITIONS FOR ACUTE MYELOID LEUKEMIA[1]

**These response criteria were defined in the context of intensive chemotherapy regimens, and may not be predictive of outcomes for patients who receive other therapies.**

- **Morphologic leukemia-free state (MLFS)**
  - **BM <5% blasts in an aspirate with spicules; at least 200 cells must be enumerated**
  - **No blasts with Auer rods or persistence of extramedullary disease**
  - **If there is a question of residual leukemia, a BM aspirate/biopsy should be repeated in one week.**
  - **A BM biopsy should be performed if spicules are absent from the aspirate sample.**
- **Complete response (CR)**
  - **Morphologic CR – transfusion independence**
  - **ANC >1000/mcL (blasts <5%)**
    - **Platelets ≥100,000/mcL (blasts <5%)**
  - **CR without MRD ($CR_{MRD-}$)**
    - **If studied pretreatment, CR with negativity for a genetic marker by RT-PCR or CR with negativity by MFC[2]**
    - **Sensitivity varies by marker and method used; analyses should be done in experienced laboratories.**
    - **Molecular CR – molecular studies negative**
  - **CR partial hematologic recovery (CRh), defined as <5% blasts in the BM, no evidence of disease (NED), and partial recovery of peripheral blood counts (platelets >50 × $10^9$/L and ANC >0.5 × $10^9$/L)[3]**
  - **CR with incomplete hematologic recovery (CRi) – All CR criteria and transfusion independence but with persistence of neutropenia (<1,000/mcL) or thrombocytopenia (<100,000/mcL).**
  - **Responses less than CR may still be meaningful depending on the therapy.**
- **Partial remission (PR)[4]**
  - **Decrease of at least 50% in the percentage of blasts to 5% to 25% in the BM aspirate and the normalization of blood counts, as noted above.**
- **Relapse following CR is defined as reappearance of leukemic blasts in the peripheral blood or the finding of more than 5% blasts in the BM, not attributable to another cause (eg, BM regeneration after consolidation therapy) or extramedullary relapse.**
- **Lack of response to induction – Inability to attain CR or CRi following exposure to at least 2 courses of intensive induction therapy.**

[1] Döhner H, Estey E, Grimwade D, et al. Diagnosis and management of AML in adults: 2017 ELN recommendations from an international expert panel. Blood 2017;129:424-447.

[2] This is clinically relevant in APL and Ph+ leukemia, and inability to achieve a significant reduction (eg >3 log) in molecular evidence of t(8;21) or inv(16) has a very high predictive value of relapse. Molecular remission for APL should be performed after consolidation, not after induction as in non-APL AML. *NPM1* is a target that can be included in the molecular response assessment. Ivey A, Hills RK, Simpson MA, et al. Assessment of minimal residual disease in standard-risk AML. N Engl J Med 2016;374:422-433.

[3] Bloomfield CD, Estey E, Pleyer L, et al. Time to repeal and replace response criteria for acute myeloid leukemia? Blood Rev 2018;32:416-425.

[4] Partial remissions are useful in assessing potential activity of new investigational agents, usually in phase I trials.

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## THERAPY FOR RELAPSED/REFRACTORY DISEASE[a]

### Clinical trial[a]

**Targeted therapy:**

- **Therapy for AML with *FLT3*-ITD mutation**
  - **Gilteritinib[1] (category 1)**
  - **HMAs(azacitidine or decitabine) + sorafenib[2,3]**
- **Therapy for AML with *FLT3*-TKD mutation**
  - **Gilteritinib[1] (category 1)**
- **Therapy for AML with *IDH2* mutation**
  - **Enasidenib[4]**
- **Therapy for AML with *IDH1* mutation**
  - **Ivosidenib[5]**
  - **Olutasidenib[6]**
- **Therapy for CD33-positive AML**
  - **Gemtuzumab ozogamicin[7]**

**Aggressive therapy for appropriate patients:**

- **Cladribine + cytarabine + G-CSF[b] ± mitoxantrone or idarubicin[8,9]**
- **HiDAC (if not received previously in treatment) ± (idarubicin or daunorubicin or mitoxantrone)[10]**
- **Fludarabine + cytarabine + G-CSF[b] ± idarubicin[11,12]**
- **Etoposide + cytarabine ± mitoxantrone[13]**
- **Clofarabine ± cytarabine ± idarubicin[14,15]**

**Less aggressive therapy:**

- **HMAs (azacitidine or decitabine)**
- **LDAC (category 2B)**
- **(HMA or LDAC)[16,17] + venetoclax[c]**

[a] There are promising ongoing clinical trials investigating targeted therapies based on molecular mutations for relapsed/refractory disease. Molecular profiling should be considered if not done at diagnosis, or repeated to determine clonal evolution. See Discussion.

[b] An FDA-approved biosimilar is an appropriate substitute for filgrastim.

[c] See Principles of Venetoclax Use With HMA in AML Patients with AML (AML-K).

[1] Perl AE, Altman JK, Cortes J, et al. Selective inhibition of *FLT3* by gilteritinib in relapsed or refractory acute myeloid leukaemia: a multicentre, first-in-human, open-label, phase 1-2 study. Lancet Oncol 2017;18:1061-1075.

[2] Ravandi F, Alattar ML, Grunwald MR, et al. Phase 2 study of azacytidine plus sorafenib in patients with acute myeloid leukemia and *FLT3* internal tandem duplication mutation. Blood 2013:121:4655-4662.

[3] Muppidi MR, Portwood S, Griffiths EA, et al. Decitabine and sorafenib therapy in *FLT3* ITD-mutant acute myeloid leukemia. Clin Lymphoma Myeloma Leuk 2015;15 Suppl:S73-9.

[4] Stein EM, DiNardo CD, Pollyea DA, et al. Enasidenib in mutant *IDH2* relapsed or refractory acute myeloid leukemia. Blood 2017;130:722-731.

[5] DiNardo CD, Stein EM, de Botton S, et al. Durable remissions with ivosidenib in *IDH1*-mutated relapsed or refractory AML. N Eng J Med 2018;378:2386-2398.

[6] Cortes J, Fenaux P, Yee K, et al. Olutasidenib (FT-2102) induces durable complete remissions in patients with relapsed/refractory mIDH1 acute myeloid leukemia. Results from a planned interim analysis of a phase 2 pivotal clinical trial [abstract] Blood 2022;140: Abstract 2757.

[7] Taksin AL, Legrand O, Raffoux E, et al. High efficacy and safety profile of fractionated doses of Mylotarg as induction therapy in patients with relapsed acute myeloblastic leukemia: a prospective study of the alfa group. Leukemia 2007;21:66-71.

[8] Robak T, Wrzesień-Kuś A, Lech-Marańda E, et al. Combination regimen of cladribine (2-chlorodeoxyadenosine), cytarabine and G-CSF (CLAG) as induction therapy for patients with relapsed or refractory acute myeloid leukemia. Leuk Lymphoma 2000;39:121-129.

[9] Fridle C, Medinger M, Wilk MC, et al. Cladribine, cytarabine and idarubicin (CLA-Ida) salvage chemotherapy in relapsed acute myeloid leukemia (AML). Leuk Lymphoma 2017:1068-1075.

[10] Karanes C, Kopecky KJ, Head DR, et al. A phase III comparison of high dose ARA-C (HIDAC) versus HIDAC plus mitoxantrone in the treatment of first relapsed or refractory acute myeloid leukemia Southwest Oncology Group Study. Leuk Res 1999;23:787-794.

[11] Montillo M, Mirto S, Petti MC, et al. Fludarabine, cytarabine, and G-CSF (FLAG) for the treatment of poor risk acute myeloid leukemia. Am J Hematol 1998;58:105-109.

[12] Parker JE, Pagliuca A, Mijovic A, et al. Fludarabine, cytarabine, G-CSF and idarubicin (FLAG-IDA) for the treatment of poor-risk myelodysplastic syndromes and acute myeloid leukaemia. Br J Haematol 1997;99:939-944.

[13] Nair G, Karmali G, Gregory SA, et al. Etoposide and cytarabine as an effective and safe cytoreductive regimen for relapsed or refractory acute myeloid leukemia. J Clin Oncol 2011;29:15_suppl, 6539-6539.

[14] Faderl S, Wetzler M, Rizzieri D, et al. Clorarabine plus cytarabine compared with cytarabine alone in older patients with relapsed or refractory acute myelogenous leukemia: results from the CLASSIC I Trial. J Clin Oncol 2012;30:2492-2499.

[15] Faderl S, Ferrajoli A, Wierda W, et al. Clofarabine combinations as acute myeloid leukemia salvage therapy. Cancer 2008;113:2090-2096.

[16] Aldoss I, Yang D, Aribi A, et al. Efficacy of the combination of venetoclax and hypomethylating agents in relapsed/refractory acute myeloid leukemia. Haematologica 2018;103:e404-e407.

[17] DiNardo CD, Rausch CR, Benton C, 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 2018;93:401-407.

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## PRINCIPLES OF VENETOCLAX USE WITH HMA OR LDAC (1 OF 2)

**General**

- The maximum number of cycles for these regimens is unknown, and treatment may continue as long as tolerated and effective. As data become available, additional insight and guidance about the recommended length of treatment will be provided.
- Patients with disease in remission should take breaks between treatment, such as extending cycle length from 28-day to 42-day cycles.
- Where there are delays in count recovery, reduction in duration of venetoclax and/or reduction in dose or duration of HMA or LDAC should be considered.[a]
- Refer to prescribing information and consult with a pharmacist for potential drug interactions (eg, CYP3A4 inhibitors).
  - Strong CYP3A4 inhibitors (especially posaconazole) require significant dose reductions during initiation and ramp-up phase followed by a reduced daily dose.
  - The use of strong or moderate CYP3A4 inducers (eg, carbamazepine, phenytoin, rifampin) should be avoided.
- The addition of a third agent is not recommended to the combinations described in this section outside the context of a clinical trial.

**Therapy for Patients with Newly Diagnosed Disease**[1]

- Prior to Therapy
  - To decrease the risk of severe tumor lysis syndrome (TLS), aim to achieve WBC count of <25,000/mcL with hydroxyurea/leukapheresis if necessary.
  - Initiate both therapies of the combination concomitantly.
  - If azole antifungal prophylaxis or other CYP enzyme-interacting medications are concurrently indicated, reduce venetoclax dose accordingly.[b]
- First Cycle Considerations
  - TLS monitoring:
    - ◊ In-patient treatment is strongly recommended during first cycle of treatment, especially through dose escalation.[c]
    - ◊ Intrapatient dose escalation for venetoclax with HMA is 100 mg, 200 mg, and 400 mg daily on days 1–3; intrapatient dose escalation for venetoclax with LDAC target dose is 100 mg, 200 mg, 400 mg, and 600 mg daily on days 1–4. Concomitant interacting medications may require changes to these dosages.[b]
    - ◊ Recommend treatment with allopurinol or other uric acid lowering agent until no further risk of TLS.
    - ◊ For patients with proliferative disease, monitor blood chemistries every 6–8 hours after initiation; if within normal limits, recheck once daily and continue monitoring until no further risk of TLS.
    - ◊ Aggressively monitor and manage electrolyte imbalances.
  - Continue treatment regardless of cytopenias; transfuse as needed and no growth factors until treatment cycle is complete.
  - BM biopsy for response assessment on days 21–28[d]
    - ◊ If no morphologic remission (persistent BM blasts above 5%) but evidence of efficacy exists, proceed with a second cycle without interruption with the goal of achieving morphologic remission, and repeat BM biopsy on days 21–28 of this cycle.
  - If blasts <5%, hold both therapies and consider the following measures:
    - ◊ Administer growth factor support if indicated.
    - ◊ Monitor blood counts for up to a 14-day period.
      - – If counts have recovered to a clinically significant threshold, resume the next cycle.
      - – If counts have not recovered to a clinically significant threshold, consider repeating the BM exam. If morphologic remission is ongoing, can continue to hold therapy for count recovery or start the second cycle with adjustment in the dose or schedule of the HMA/LDAC and/or venetoclax.

Footnotes on AML-K 2 of 2
Continued

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## PRINCIPLES OF VENETOCLAX USE WITH HMA OR LDAC (2 OF 2)

**Therapy for Patients with Newly Diagnosed Disease (Continued)**[1]

- **Cycle 2 and beyond**
  - **If NED after cycle 1, repeat BM biopsy at 3- to 6-month intervals, assuming no unexpected changes in blood counts occur.**
  - **If remission after cycle 1, continue sequential cycles with up to 14-day interruptions between cycles for count recovery and/or growth factor support.**
  - **If persistent disease after cycle 1, repeat BM biopsy following cycle 2 (or subsequent cycles until NED or remission) to again assess for cellularity and disease response, and to determine timing of subsequent cycle.**
  - **If count recovery worsens over time, rule out relapsed disease with repeat BM biopsy. If a morphologic remission is ongoing with worsening blood counts, consider decreasing the dose/schedule of venetoclax and/or HMA/LDAC.**
  - **Repeat BM biopsy when concerned about relapse.**
  - **If no morphologic remission after cycle 2 or 3, the likelihood of response is decreased and patients could consider enrollment in a clinical trial if available. In the absence of available clinical trials, if the patient's disease has had any response with manageable toxicity, continue therapy as tolerated.**

**Therapy for Patients with Relapsed/Refractory Disease**

- **Recommend antifungal prophylaxis if indicated.**[2]
- **Consider the same TLS and intrapatient dose escalation measures as described under "First Cycle Considerations."**
- **Consider the same recommendations for early BM biopsy and cytopenia mitigation plan proposed under "First Cycle Considerations."**

[a] Recommend referral to tertiary care center/academic medical center if need to consider discontinuation of any agent, or to continue maintenance on single-agent venetoclax.
[b] See venetoclax prescribing information: https://www.accessdata.fda.gov/drugsatfda_docs/label/2022/208573s027lbl.pdf
[c] Patients may need hospitalization beyond first cycle, based on medical circumstances. Treatment in outpatient setting may be considered per institutional practice or treatment preference.
[d] Combination of venetoclax + decitabine may favor an earlier assessment at day 21 (if blasts are reduced, but no morphologic remission).

[1] Jonas BA, Pollyea DA. How we use venetoclax with hypomethylating agents for the treatment of newly diagnosed patients with acute myeloid leukemia. Leukemia 2019;33:2795-2804.
[2] Aldoss I, Dadwal S, Zhang J, et al. Invasive fungal infections in acute myeloid leukemia treated with venetoclax and hypomethylating agents. Blood Adv 2019;3:4043-4049.

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## INTRODUCTION

Decisions about diagnosis and management for BPDCN should involve multidisciplinary consultation at a high-volume center with use of appropriate interventions. Consider referral to an academic institution.

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# NCCN Guidelines Version 3.2023
# Blastic Plasmacytoid Dendritic Cell Neoplasm (Age ≥18 years)

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## EVALUATION/WORKUP FOR BPDCN[a,1]

- H&P
- CBC, platelets, differential, CMP
- Analysis of skin lesions (collaboration with dermatology is recommended),[2] peripheral blasts, BM aspirate/biopsy, and lymph node biopsy including:
  - Dendritic cell morphology assessment
  - IHC
  - Flow cytometry
  - Cytogenetic analysis (karyotype and/or FISH)
  - Molecular analysis (most common aberrations include: *ASXL1*, *IDH1–2*, *IKZF1–3*, *NPM1*, *NRAS*, *TET1–2*, *TP53*, *U2AF1*, *ZEB2*)[3]
- PET/CT scan of other sites, if clinical suspicion for extramedullary disease and/or lymphadenopathy
- All patients require a diagnostic LP at the time of initial diagnosis, at disease relapse, or any other time when there is a clinical suspicion for CNS involvement. Follow with IT chemotherapy prophylaxis as clinically indicated (see BPDCN-B).

## DIAGNOSIS[3]

BPDCN diagnosis requires at least 4 of 6 BPDCN antigens:
- CD123
- CD4
- CD56
- TCL-1
- CD2AP
- CD303/BDCA-2

without myeloid,[b] T or B lineage expression markers

→ BPDCN confirmed → See Treatment Induction (BPDCN-2)

[a] See Principles of BPDCN (BPDCN-A).

[b] Myeloid markers include myeloperoxidase (MPO), lysozyme, CD14, CD34, CD116, and CD163.

[1] Facchetti F, Petrella T, Pileri SA. Blastic plasmacytoid dendritic cell neoplasm. In: Swerdlow SH, Campo E, Harris NL, et al. WHO Classification of Tumours of Haematopoietic and Lymphoid Tissues. Revised 4th ed. IARC Press: Lyon 2017:173-177.

[2] Pemmaraju N, et al. N Engl J Med 2019;380:1628-1637. Close collaboration with dermatology is recommended. For guidance on classification and measurement of skin lesions, see page MFSS-3 in the NCCN Guidelines for Primary Cutaneous Lymphomas.

[3] Menezes J, et al. Leukemia 2014;28:823-829

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## TREATMENT OF BPDCN[c]

BPDCN

- Candidate for intensive remission induction therapy
- Patients with low performance and/or nutritional status (ie, serum albumin <3.2 g/dL; not a candidate for intensive remission induction therapy or tagraxofusp-erzs[d])

## TREATMENT INDUCTION[4]

- Tagraxofusp-erzs[d] (formerly SL-401) (preferred)
  12 mcg/kg IV over 15 minutes once daily on days 1–5 of a 21-day cycle[5,6]
  - For management of adverse events, see Supportive Care (BPDCN-C)
- Chemotherapy[d]
  - AML-type induction chemotherapy:
    Standard-dose cytarabine 100–200 mg/m² continuous infusion x 7 days with idarubicin 12 mg/m² or daunorubicin 60–90 mg/m² x 3 days[7]
  - ALL-type induction chemotherapy:
    HyperCVAD regimen (hyperfractionated cyclophosphamide, vincristine, doxorubicin, dexamethasone, alternating with high-dose methotrexate and cytarabine)[7,8,9]
  - Lymphoma induction:
    CHOP regimen (cyclophosphamide, doxorubicin, vincristine, and prednisone)[7]
- IT chemotherapy in patients with documented CNS disease at diagnosis/ if clinically indicated (methotrexate, cytarabine)

CR[e]
- Consider
  - Allogeneic HCT[7,10,11,12]
  - Autologous HCT
  → See Surveillance (BPDCN-3)
- Tagraxofusp-erzs[d] until progression

Lack of response to induction[9] → See Treatment for Relapsed/Refractory Disease (BPDCN-3)

Localized/isolated cutaneous disease → Palliative options include:
- Surgical excision
- Focal RT

Systemic disease (palliative intent) → Options include:
- Venetoclax-based therapy,[13] see AML-5
- Systemic steroids
- Supportive Care (BPDCN-C)

[c] See Principles of Supportive Care for BPDCN (BPDCN-C).
[d] Consider CNS prophylaxis for patients with overt systemic disease.
[e] CR in BPDCN has the same hematologic criteria as AML (See AML-I), but it is also important to document resolution of any extramedullary sites including CNS and skin lesions. If the skin still shows microscopic disease , consider continuing additional cycles (at least 4) of therapy before managing as relapsed/refractory disease. For appropriate studies to assess CR, see Pemmaraju N, et al. N Engl J Med 2019;380:1628-1637.

[4] Pemmaraju N, et al. Blood 2019;134(Supplement_1):2723.
[5] Frankel AE, et al. Blood 2014;124:385-392.
[6] Pemmaraju N, et al. N Engl J Med 2019;380:1628-1637.
[7] Pagano L, et al. Haematologica 2013;98:239-246.
[8] Reimer P, et al. Bone Marrow Transplant 2003;32:637-646.
[9] Deotare U, et al. Am J Hematol 2016;91:283-286.
[10] Kharfan-Dabaja MA, et al. Br J Haematol 2017;179:781-789.
[11] Roos-Weil D, et al. Blood 2013;121:440-446.
[12] Aoki T, et al. Blood 2015;125:3559-3562.
[13] DiNardo CD, et al. Am J Hematol 2018;93:401-407.

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# NCCN Guidelines Version 3.2023
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## SURVEILLANCE

- CBC, platelets every 1–3 mo for 2 y, then every 3–6 mo up to 5 y
- BM aspirate and biopsy only if peripheral smear is abnormal or cytopenias develop
- Repeat PET/CT scan for patients with prior evidence of extramedullary disease
- Consider re-biopsy for any suspicious skin or extramedullary lesions

→ Relapsed/ refractory BPDCN →

## TREATMENT FOR RELAPSED/REFRACTORY DISEASE

- Evaluate CNS for disease/prophylaxis[14]
- Consider
  - Clinical trial (preferred)
  - Tagraxofusp-erzs[d,6] (preferred, if not already used)
    For management of adverse events, see Supportive Care (BPDCN-C)
  - Chemotherapy (if not already used), see Treatment Induction (BPDCN-2)
  - Local RT to isolated lesions/areas
  - Systemic steroids
  - Venetoclax-based therapy,[13,15,16] see AML-5
- Donor search should be initiated at first relapse in appropriate patients concomitant with institution of other therapy if no sibling donor has been identified

[6] Pemmaraju N, et al. N Engl J Med 2019;380:1628-1637.
[13] DiNardo CD, et al. Am J Hematol 2018;93:401-407.
[14] Martin-Martin L, et al. Oncotarget 2016;7:10174-10181.
[15] Montero J, et al. Cancer Discovery 2017;7:156-164.
[16] Rausch CR, et al. Blood 2017;130:1356.

[d] Consider CNS prophylaxis for patients with overt systemic disease.

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# NCCN Guidelines Version 3.2023
# Blastic Plasmacytoid Dendritic Cell Neoplasm (Age ≥18 years)

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## PRINCIPLES OF BPDCN

**General Principles:**

- **BPDCN is a disorder of immature dendritic cells that regulate effector T-cell function.**
- **It constitutes only 0.44% of hematologic malignancies and <1% of acute leukemia presentations.[1]**
- **It occurs in all races and geographic areas.**
- **It is more common in adults (median age, 65–67 years) with an approximate male-to-female ratio of 3:1.**
- **It most commonly presents as asymptomatic skin lesions,[a,2] cytopenias, circulating peripheral blasts (leukemic phase), lymphadenopathy, and CNS manifestations.**
- **Prognosis for BPDCN is poor and the median OS is approximately 8–12 months when patients are treated with chemotherapy.[3,4]**
- **Studies suggest that being in first remission during receipt of allogeneic HCT significantly enhances the median OS.[4-6] Reduced-intensity conditioning may be considered in patients whose disease achieves CR but cannot tolerate myeloablative HCT.[7]**
- **For fit patients, current treatment options for BPDCN include tagraxofusp-erzs and chemotherapy, whereas those with low albumin and/or comorbidities should receive localized therapy or supportive care as shown in the algorithm (see BPDCN-2).**
  - **Hypoalbuminemia and capillary leak syndrome are known, potentially serious adverse events associated with tagraxofusp-erzs treatment,[8] and must be monitored closely during therapy (see Principles of Supportive Care for BPDCN [BPDCN-C]).**

[a] Close collaboration with dermatology is recommended. For guidance on classification and measurement of skin lesions, see page MFSS-3 in the NCCN Guidelines for Primary Cutaneous Lymphomas.

[1] Bueno C, Almeida J, Lucio P, et al. Incidence and characteristics of CD4(+)/HLA DRhi dendritic cell malignancies. Haematologica 2004;89:58-69.
[2] Pemmaraju N, Lane AA, Sweet KL, et al. Tagraxofusp in blastic plasmacytoid dendritic-cell neoplasm. N Engl J Med 2019;380:1628-1637. 3 Dalle S, Beylot-Barry M, Bagot M, et al. Blastic plasmacytoid dendritic cell neoplasm: is transplantation the treatment of choice? Br J Dermatol 2010;162:74-79.
[4] Pagano L, Valentini CG, Pulsoni A, et al. Blastic plasmacytoid dendritic cell neoplasm with leukemic presentation: an Italian multicenter study. Haematologica 2013;98:239-246.
[5] Deotare U, Yee KW, Le LW, et al. Blastic plasmacytoid dendritic cell neoplasm with leukemic presentation: 10-Color flow cytometry diagnosis and HyperCVAD therapy. Am J Hematol 2016;91:283-286.
[6] Roos-Weil D, Dietrich S, Boumendil A, et al. Stem cell transplantation can provide durable disease control in blastic plasmacytoid dendritic cell neoplasm: a retrospective study from the European Group for Blood and Marrow Transplantation. Blood 2013;121:440-446.
[7] Pagano L, Valentini CG, Grammatico S, Pulsoni A. Blastic plasmacytoid dendritic cell neoplasm: diagnostic criteria and therapeutical approaches. Br J Haematol 2016;174:188-202.
[8] Frankel AE, Woo JH, Ahn C, et al. Activity of SL-401, a targeted therapy directed to interleukin-3 receptor, in blastic plasmacytoid dendritic cell neoplasm patients. Blood 2014;124:385-392.

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National Comprehensive Cancer Network®

# NCCN Guidelines Version 3.2023
# Blastic Plasmacytoid Dendritic Cell Neoplasm (Age ≥18 years)

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## EVALUATION AND TREATMENT OF CNS DISEASE

**With CNS disease →**

- **CNS-directed IT chemotherapy[a]**
  - **Twice weekly dosing until CSF is clear**
  - **Once the CSF is clear (negative on cytology) continue weekly IT treatments for at least 4 doses, then twice per month for a total of at least 8 doses**
  - **IT treatments may be continued once or twice per month, if desired**

**Without CNS disease →**

- **CNS-directed IT chemotherapy[a] strongly recommended to be administered prophylactically**
  - **Twice per month for a total of at least 8 doses**
  - **IT treatment may be continued once or twice per month, if desired**

[a] Chemotherapy regimens may follow institutional standards, but would preferably be aggressive including alternating cytarabine with methotrexate, or triple IT agents (ie, cytarabine, methotrexate, steroid).

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## PRINCIPLES OF SUPPORTIVE CARE FOR BPDCN

**Administration/Management of Toxicities Associated with Tagraxofusp-erzs**[a]

- Patients must have a baseline serum albumin of 3.2 g/dL or higher to be able to start tagraxofusp-erzs.
  - Replace serum albumin if <3.5 g/dL or if there is a reduction of ≥0.5 from baseline.
- Capillary leak syndrome (life-threatening/fatal) can occur in patients receiving this drug.
- The first cycle of this drug should be administered in the inpatient setting. Closely monitor toxicity during and after drug administration. It is recommended that patients remain in the hospital for at least 24 hours after completion of the first cycle.
  - Premedicate with an H1-histamine antagonist, acetaminophen, corticosteroid, and H2-histamine antagonist prior to each infusion.
  - Administer tagraxofusp-erzs at 12 mcg/kg IV over 15 minutes once daily on days 1–5 of a 21-day cycle. Alternately, 5 doses can be administered over a 10-day period, if needed for dose delays.
- Prior to each dose of drug: Check vital signs, albumin, transaminases, and creatinine.
- Collaboration with a dermatologist for supportive care is essential.

**Hold Tagraxofusp-erzs Dosing for the Following Reasons:**

- Serum albumin <3.5 g/dL or a reduction from baseline of ≥0.5
- Body weight ≥1.5 kg over prior day
- Edema, fluid overload, and/or hypotension
- Alanine aminotransferase (ALT)/aspartate aminotransferase (AST) increase >5 times the upper limit of normal
- Serum creatinine >1.8 or CrCl ≤60 mL/min
- Systolic blood pressure (SBP) ≥160 or ≤80 mmHg
- Heart rate (HR) ≥130 bpm or ≤40 bpm
- Temperature ≥38°C
- Mild to severe hypersensitivity reaction

[a] For full details on administration and toxicity management, see: https://www.accessdata.fda.gov/drugsatfda_docs/label/2022/761116s007lbledt.pdf

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## ABBREVIATIONS

| | |
|---|---|
| aGVHD | acute graft-versus-host disease |
| ALAL | acute leukemia of ambiguous lineage |
| ALT | alanine aminotransferase |
| AMC | academic medical center |
| AML | acute myeloid leukemia |
| ANC | absolute neutrophil count |
| APL | acute promyelocytic leukemia |
| AST | aspartate aminotransferase |
| ATRA | all-trans retinoic acide |
| BM | bone marrow |
| BPDCN | blastic plasmacytoid dendritic cell neoplasm |
| BUN | blood urea nitrogen |
| bZIP | basic leucine zipper |
| CBC | complete blood count |
| CBF | core binding factor |
| CHIP | clonal hematopoiesis of indeterminate potential |
| CMML | chronic myelomonocytic leukemia |
| CMP | comprehensive metabolic panel |
| CMV | Cytomegalovirus |
| CNS | central nervous system |
| CNV | copy number variant |
| CR | complete response |
| CR1 | first complete response |
| CRc | microscopic disease |
| CrCl | creatinine clearance |
| CRh | complete response with partial hematologic recovery |
| CRi | complete response with incomplete hematologic recovery |
| CRMRD- | CR without MRD |
| CSF | cerebrospinal fluid |
| DIC | disseminated intravascular coagulation |
| ECG | electrocardiogram |
| EF | ejection fraction |
| ESA | erythropoiesis-stimulation agent |
| FISH | fluorescence in situ hybridization |
| FNA | fine-needle aspiration |
| G6PD | Glucose-6-phosphate dehydrogenase |
| G-CSF | granulocyte colony-stimulating factor |
| GI | gastrointestinal |
| GM-CSF | granulocyte-macrophage colony-stimulating factor |
| HCT | hematopoietic cell transplantation |
| HiDAC | high-dose cytarabine |
| HLA | human leukocyte antigen |
| HMA | hypomethylating agent |
| HP | histroy and physical |
| HR | heart rate |
| IHC | immunohistochemistry |
| IT | intrathecal |
| ITD | internal tandem duplication |
| LDAC | Low-dose cytarabine |
| LDH | lactate dehydrogenase |
| LFT | liver function tests |
| LP | lumbar puncture |
| MDS | myelodysplastic syndrome |
| MFC | multicolor flow cytometry |
| MLFS | morphologic leukemia-free state |
| MPAL | mixed phenotype acute leukemia |
| MPO | myeloperoxidase |
| MRC | myelodysplasia-related changes |
| MRD | measurable (minimal) residual disease |
| NED | no evidence of disease |
| NGS | next-generation sequencing |
| NOS | not otherwise specified |
| OS | overall survival |
| PCR | polymerase chain reaction |
| PR | partial remission |
| PT | prothrombin time |
| PTD | partial tandem duplication |
| PTT | partial thromboplastin time |
| RBC | red blood cell |
| RT | radiation therapy |
| RQ-PCR | real-time quantitative PCR |
| RT-PCR | real-time PCR |
| SBP | systolic blood pressure |
| SC | subcutaneously |
| SOS | sinusoidal obstruction syndrome |
| TKD | tyrosine kinase domain |
| TLS | tumor lysis syndrome |
| TPO | thrombopoietin |
| WBC | white blood cell |

| NCCN Categories of Evidence and Consensus | |
|---|---|
| **Category 1** | Based upon high-level evidence, there is uniform NCCN consensus that the intervention is appropriate. |
| **Category 2A** | Based upon lower-level evidence, there is uniform NCCN consensus that the intervention is appropriate. |
| **Category 2B** | Based upon lower-level evidence, there is NCCN consensus that the intervention is appropriate. |
| **Category 3** | Based upon any level of evidence, there is major NCCN disagreement that the intervention is appropriate. |

All recommendations are category 2A unless otherwise indicated.

| NCCN Categories of Preference | |
|---|---|
| **Preferred intervention** | Interventions that are based on superior efficacy, safety, and evidence; and, when appropriate, affordability. |
| **Other recommended intervention** | Other interventions that may be somewhat less efficacious, more toxic, or based on less mature data; or significantly less affordable for similar outcomes. |
| **Useful in certain circumstances** | Other interventions that may be used for selected patient populations (defined with recommendation). |

All recommendations are considered appropriate.

 

National Comprehensive Cancer Network®

# NCCN Guidelines Version 3.2023
# Acute Myeloid Leukemia

## Discussion

This discussion corresponds to the NCCN Guidelines for Acute Myeloid Leukemia. Last updated: April 5, 2023

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## Overview

Acute myeloid leukemia (AML) is a heterogeneous hematologic malignancy characterized by the clonal expansion of myeloid blasts in the peripheral blood, bone marrow, and/or other tissues. It is the most common form of acute leukemia among adults and accounts for the largest number of annual deaths from leukemias in the United States. An estimated 19,940 people will be diagnosed with AML in 2020, and 11,180 patients will die of the disease.[1] According to the SEER Cancer Statistics Review, the median age at diagnosis is 68 years;[2] other registries report 71 years,[3] with approximately 54% of patients diagnosed at ≥65 years of age (and approximately a third diagnosed at ≥75 years of age).[2] Thus, as the population ages, the incidence of AML, along with myelodysplastic syndromes (MDS), seems to be rising.

Environmental factors that have long been established to increase the risks of MDS and AML include prolonged exposure to petrochemicals; solvents such as benzene; pesticides; and ionizing radiation.[4]

Therapy-related MDS/AML (secondary MDS/AML) is a well-recognized consequence of cancer treatment in a proportion of patients receiving cytotoxic therapy for solid tumors or hematologic malignancies. Reports suggest that therapy-related MDS/AML may account for 5% to 20% of patients with MDS/AML.[5-7] The rate of therapy-related MDS/AML is higher among patients with certain primary tumors, including breast cancer, gynecologic cancers, and lymphomas (both non-Hodgkin lymphoma and Hodgkin lymphoma), largely owing to the more leukemogenic cytotoxic agents that are commonly used in the treatment of these tumors.[7-10] Two well-documented categories of cytotoxic agents associated with the development of therapy-related MDS/AML are alkylating agents and topoisomerase inhibitors.[5,8,9] Treatment with antimetabolites, such as the purine analog fludarabine, has also been associated with therapy-related MDS/AML in patients with lymphoproliferative disorders, particularly when administered in combination with alkylating agents.[11,12] Radiotherapy, especially in the context of myeloablative therapy (eg, total body irradiation or radioimmunotherapy) given before autologous hematopoietic cell transplantation (HCT) may also increase the risk for therapy-related MDS/AML.[13,14] The disease course of therapy-related MDS/AML is generally progressive and may be more resistant to conventional cytotoxic therapies than *de novo* cases of MDS/AML.[9] Importantly, clinical outcomes in patients with therapy-related AML have been shown to be significantly inferior (both in terms of relapse-free survival [RFS] and overall survival [OS]) compared with patients with de novo cases,[8,15] except those with the therapy-related acute promyelocytic leukemia (APL) subtype[7,16] or the favorable-risk core binding factor (CBF) translocations. The proportion of patients with unfavorable cytogenetics tends to be higher in the population with therapy-related AML. Even among the subgroup with favorable karyotypes, those with therapy-related AML tend to do less well.

The AML Panel for the NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) convenes annually to update recommendations for the diagnosis and treatment of AML in adults. These recommendations are based on a review of recently published clinical trials that have led to significant improvements in treatment or have yielded new information regarding biologic factors that may have prognostic importance.

## Guidelines Update Methodology

The complete details of the Development and Update of the NCCN Guidelines are available at www.NCCN.org.

## Literature Search Criteria

Prior to the update of the NCCN Guidelines® for AML, an electronic search of the PubMed database was performed to obtain key literature in AML published since the previous Guidelines update using the following search terms: acute myeloid leukemia or acute promyelocytic leukemia. The

PubMed database was chosen as it remains the most widely used resource for medical literature and indexes peer-reviewed biomedical literature.[17]

The search results were narrowed by selecting studies in humans published in English. Results were confined to the following article types: Clinical Trial, Phase II; Clinical Trial, Phase III; Clinical Trial, Phase IV; Guideline; Meta-Analysis; Randomized Controlled Trial; Systematic Reviews; and Validation Studies.

The data from key PubMed articles as well as articles from additional sources deemed as relevant to these Guidelines and discussed by the panel have been included in this version of the Discussion section (eg, e-publications ahead of print, meeting abstracts). Recommendations for which high-level evidence is lacking are based on the panel's review of lower-level evidence and expert opinion.

## Sensitive/Inclusive Language Usage

NCCN Guidelines strive to use language that advances the goals of equity, inclusion, and representation. NCCN Guidelines endeavor to use language that is person-first; not stigmatizing; anti-racist, anti-classist, anti-misogynist, anti-ageist, anti-ableist, and anti-fat-biased; and inclusive of individuals of all sexual orientations and gender identities. NCCN Guidelines incorporate non-gendered language, instead focusing on organ-specific recommendations. This language is both more accurate and more inclusive and can help fully address the needs of individuals of all sexual orientations and gender identities. NCCN Guidelines will continue to use the terms men, women, female, and male when citing statistics, recommendations, or data from organizations or sources that do not use inclusive terms. Most studies do not report how sex and gender data are collected and use these terms interchangeably or inconsistently. If sources do not differentiate gender from sex assigned at birth or organs present, the information is presumed to predominantly represent cisgender individuals. NCCN encourages researchers to collect more specific data in future studies and organizations to use more inclusive and accurate language in their future analyses.

## Initial Evaluation

The initial evaluation of AML has two objectives. The first is to characterize the disease process based on factors such as prior toxic exposure, antecedent myelodysplasia, and karyotypic and molecular abnormalities, which may provide prognostic information that can impact responsiveness to chemotherapy and risk of relapse. The second objective focuses on patient-specific factors, including assessment of comorbid conditions, which may affect an individual's ability to tolerate chemotherapy. Both disease-specific and individual patient factors are taken into consideration when deciding treatment.

### Workup

The evaluation and initial workup for suspected AML consists of a comprehensive medical history and physical examination. Laboratory evaluations include a comprehensive metabolic panel and a complete blood count (CBC) including platelets and a differential of white blood cells (WBCs). Serum uric acid and lactate dehydrogenase (LDH) have prognostic relevance and should be evaluated.[18,19] Bone marrow core biopsy and aspirate analyses (including immunophenotyping by immunohistochemistry stains with flow cytometry) and cytogenetic analyses (karyotype with fluorescence in situ hybridization [FISH]) are necessary for risk stratification and to potentially guide therapy of AML. Several gene mutations are associated with specific prognoses in a subset of patients (category 2A) and may guide treatment decisions (category 2B). Presently, *c-KIT*, *FLT3*-ITD, *FLT3*-TKD, *NPM1*, *CEBPA* (biallelic), *IDH1*/*IDH2*, *RUNX1*, *ASXL1*, *TP53*, *BCR-ABL*, and *PML-RAR* alpha are included in this group. All patients should be tested for mutations in these

genes, and multiplex gene panels and comprehensive next-generation sequencing (NGS) analysis are recommended for the ongoing management of AML and various phases of treatment.[20-22] To appropriately stratify therapy options, test results of molecular and cytogenetic analyses of immediately actionable genes or chromosomal abnormalities (eg, *CBF, FLT3* [ITD or TKD], *NPM1*, *IDH1*, or *IDH2*) should be expedited. For patients with hyperleukocytosis uncontrolled with hydroxyurea or leukapheresis, one dose of intermediate-dose cytarabine (1–2 grams)[23] may be considered prior to receiving results. For patients who prefer not to receive blood transfusions as part of therapy, see *Supportive Care for Patients with AML Who Prefer Not to Receive Blood Transfusions* for general considerations, although the committee believes that in many cases, good outcomes from this strategy are rare. If blastic plasmacytoid dendritic cell neoplasm (BPDCN) is suspected, see *Management of BPDCN* for work up, diagnosis and treatment recommendations.

Recent studies have reported on the prognostic impact of a number of molecular abnormalities in patients with AML (see *Molecular Markers and Risk Stratification*). Adequate marrow should be available at the time of diagnosis or relapse for molecular studies as per the institutional practice. Local pathologists should be consulted to discuss ways to optimize sample collection and preservation. If molecular testing is not available at the patient's treatment center, evaluation at an outside reference laboratory or transfer to another institution is recommended prior to performing the marrow evaluation. Circulating leukemic blasts from peripheral blood may alternatively be used to detect molecular abnormalities.

Extramedullary presentation, including central nervous system (CNS) disease, is uncommon in patients with AML. However, if extramedullary disease is suspected, a PET/CT is recommended. Patients with significant CNS signs or symptoms at presentation should be evaluated using appropriate imaging techniques, such as radiography, CT, or MRI for the detection of intracranial bleeding, leptomeningeal disease, or mass lesions in either the brain or spinal cord. If CNS hemorrhage is suspected, a CT of brain without contrast is recommended. If leukemic meningitis is suspected, a brain MRI with contrast is recommended. However, if symptoms persist, and bleeding and mass/lesions are excluded, the patient should have a lumbar puncture (LP) for diagnostic and possible therapeutic purposes once coagulopathy has been corrected, adequate platelet support is available, and the circulating disease has been cleared through the initiation of systemic therapy. Routine screening LPs are not warranted at the time of diagnosis in patients with AML. However, for patients at high risk for CNS disease, such as those with monocytic differentiation or high WBC count (>40,000/mcL)[24] at presentation, a diagnostic LP should be considered as part of the documentation of remission status. Screening LPs should be considered at first remission before first consolidation in the setting of monocytic differentiation, mixed phenotype acute leukemia (MPAL), WBC count >40,000/mcL at diagnosis, high-risk APL, *FLT3* mutations, or extramedullary disease, particularly in patients not receiving high-dose cytarabine (HiDAC) (ie, patients ≥60 years of age). For patients who present with solitary extramedullary disease (currently referred to as myeloid sarcoma, and historically as granulocytic sarcoma, or chloroma) without overt marrow disease, the initial treatment should still be based on systemic induction chemotherapy. Radiation or surgical resection may be incorporated with systemic chemotherapy in emergent situations; however, these modalities, if needed at all, should be optimally deferred until after count recovery to avoid excess toxicity.

Coagulopathy is common at presentation in many leukemias; it is therefore standard clinical practice to screen for coagulopathy by evaluating prothrombin time, partial thromboplastin time, and fibrinogen

activity as part of the initial evaluation and before performing any invasive procedure. The need for a cardiac evaluation (eg, echocardiogram or multigated acquisition [MUGA] scan) should be determined based on individual risk factors. Patients with a history or symptoms of cardiac disease, prior exposure to cardiotoxic drugs or thoracic radiation, or those of an older age, should have an echocardiogram. In younger patients who are otherwise asymptomatic with no history of cardiac disease, an echocardiogram can be considered. In the setting of acute illness, treatment should not be delayed for an echocardiogram. A small study of 76 patients with cancer who were screened for cardiac disease identified only 4 patients with cardiac abnormalities. Of these 4 patients, the presence of cardiac disease did not change the course of treatment.[25]

Human leukocyte antigen (HLA) typing should be performed in all patients with newly diagnosed AML for whom allogeneic HCT would be considered. HLA typing of family members is recommended for patients up to age 80 years or per institutional practice who do not have favorable-risk cytogenetics, and tissue typing should be broadened to include alternative donor searches. In patients with any non-favorable risk, a donor search should begin while the patient is undergoing induction chemotherapy rather than waiting for remission to be achieved. Early referral to a transplant center for patients with non-favorable risk AML is recommended.

### Diagnosis

Originally, the classification system for AML was defined by the French American British (FAB) system, which relied on cytochemical stains and morphology to separate AML from acute lymphoblastic leukemia (ALL) and to categorize the disease based on degree of myeloid and monocytic differentiation. In 1999, WHO developed a newer classification system, which incorporates information from cytogenetics and evidence of myelodysplasia, to refine prognostic subgroups that may define treatment strategies.[26] During this transition from the FAB system to the WHO classification, the percent blasts threshold for defining high-grade MDS and AML was lowered. The FAB classification had set the threshold between high-grade MDS and AML at 30% blasts, whereas the WHO classification lowered the threshold for diagnosing AML to 20% or more blasts. This change was based on the finding that the biologic behavior (and survival outcomes) of the FAB MDS subgroup of “refractory anemia with excess blasts in transformation (RAEB-T),” defined as patients with 20% to 30% blasts, was similar compared with that of patients with greater than 30% blasts. In an appropriate clinical setting, the WHO classification system further allowed AML to be diagnosed in patients with abnormal hematopoiesis and in the setting of characteristic clonal structural cytogenetic abnormalities with t(15;17), t(8;21), and inv(16) or t(16;16) regardless of the percentage of marrow blasts.

In 2003, the International Working Group for Diagnosis, Standardization of Response Criteria accepted the cytochemical and immunophenotypic WHO criteria as the standard for diagnosing AML, including the reporting of myelodysplasia according to morphology.[27] However, no evidence shows that myelodysplasia represents an independent risk factor, because it is frequently linked to poor-risk cytogenetics.

In 2008, WHO revised the diagnostic and response criteria for AML to include additional recurrent genetic abnormalities created by reciprocal translocations/inversions, and a new provisional category for some of the molecular markers that have been found to have a prognostic impact.[28] Additionally, the category of AML with recurrent genetic abnormalities was expanded to include the following: t(9;11)(p22;q23), t(6;9)(p23;q34) (provisional entity), inv(3)(q21 q26.2) or inv(3;3)(q21;q26.2) (provisional entity), and t(1;22)(p13;q13) (provisional entity), in addition to the previously recognized t(8;21)(q22;q22); inv(16)(p13;1q22) or t(16;16)(p13.1;q22); and t(15;17)(q22;q12) [APL subtype]. Other

provisional entities include AML with molecular abnormalities such as mutated nucleophosmin (*NPM1)* or CCAAT/enhancer-binding protein alpha (*CEBPA)* genes (further information on these genetic lesions is provided later).[28] In 2016, WHO expanded the recurrent genetic abnormalities to include two provisional categories, AML with *BCR-ABL1* rearrangement and AML with *RUNX1* mutation. AML with *BCR-ABL1* rearrangement is a rare *de novo* AML that may benefit from therapies that entail tyrosine kinase inhibitors. AML with *RUNX1* mutation is associated with a poorer prognosis.

In accordance with the 2016 WHO classification, a diagnosis of AML is made based on the presence of 20% or more blasts in the bone marrow or peripheral blood. In an appropriate clinical setting, a diagnosis of AML may be made with <20% blasts in the setting of recurrent cytogenetic abnormalities including t(15;17), t(8;21), t(16;16), or inv(16). The accurate classification of AML requires multidisciplinary diagnostic studies including morphology, immunophenotyping (immunohistochemistry and flow cytometry), and molecular genetics analysis. The latter should include a complete cytogenetic analysis and advanced molecular analysis techniques, as needed, to specify both translocations and gene mutations. The NCCN AML Panel suggests that complementary diagnostic techniques can be used at the discretion of the pathology department of the individual institution. Some cases may still show evidence of both myeloid and lymphoid antigen expression on the leukemic cells and are defined as acute leukemias of ambiguous lineage. This is further subgrouped into acute undifferentiated leukemia, MPAL with *BCR-ABL1* rearrangement, MPAL with rearranged *KMT2A*, MPAL with B-cell/myeloid features not otherwise specified, and MPAL with T-cell/myeloid features not otherwise specified. The expression of both cytochemical and/or immunophenotypic characteristics of both lineages on the same cells is defined as biphenotypic, whereas expression of lineage-specific characteristics on different populations of leukemia cells is termed bilineal. Due to the rarity of acute leukemias of ambiguous lineage (as defined by the 2016 WHO classification), consultation with an experienced hematopathologist should be sought.

Aberrant expression of differentiation antigens present at diagnosis may allow tracking of residual blasts through flow cytometry in follow-up samples that may appear normal according to conventional morphology. The use of immunophenotyping and molecular markers to monitor measurable (also known as minimal) residual disease (MRD) in adult AML has not yet been widely incorporated into postremission monitoring strategies, except in some patient subgroups with APL, CBF-AML, and *NPM1*-positive AML. However, ongoing research is moving MRD monitoring to the forefront for all patients with AML (see *Role of MRD Monitoring*).

### Cytogenetics and Risk Stratification

Although cytogenetic information is often unknown when treatment is initiated in patients with de novo AML, karyotype represents the single most important prognostic factor for predicting remission rates, relapse risks, and OS outcomes. The cytogenetic risk categories adopted by these guidelines are primarily based on analyses of large datasets from major cooperative group trials (see *Risk Stratification by Genetics in Non-APL AML* in the algorithm).[29-31] In an analysis of data from pediatric and adult patients with AML (n = 1612) enrolled in the United Kingdom Medical Research Council (UK MRC) AML 10 trial, the 5-year survival rates for those with favorable, intermediate, and unfavorable risk cytogenetics were 65%, 41%, and 14%, respectively.[30] In a review of data from adult patients treated in a phase III Southwest Oncology Group (SWOG)/Eastern Cooperative Oncology Group (ECOG) intergroup study (n = 609), the 5-year survival rates in the setting of favorable, intermediate, and adverse risk cytogenetics were 55%, 38%, and 11%, respectively.[31] Similarly, in a retrospective review of adult patients with AML treated on Cancer and

Leukemia Group B (CALGB) protocols (n = 1213), the 5-year survival rates in the setting of favorable-, intermediate-, and poor-risk cytogenetics were 55%, 24%, and 5%, respectively.[29] The AML 11 trial had similar results with 5-year survival rates in the setting of favorable-, intermediate-, and poor-risk cytogenetics of 34%, 13%, and 2%, respectively.[32] This last study included a population of patients ≥55 years of age, which is believed to attribute to the overall lower percent survival in all groups.

The importance of obtaining adequate samples of marrow or peripheral blood at diagnosis for full karyotyping and FISH cytogenetic analysis for the most common abnormalities cannot be overemphasized. Although FISH studies for common cytogenetic abnormalities may allow for rapid screening to identify either favorable- or unfavorable-risk groups, additional tests are needed to provide a full picture of the genetic factors that contribute to risk (see *Molecular Markers and Risk Stratification*).

The presence of autosomal chromosome monosomies in AML has emerged as an important prognostic factor associated with extremely poor prognosis.[33-35] Data from three large studies have identified monosomal karyotypes (defined as ≥2 autosomal monosomies, or a single monosomy with an additional structural abnormality) as a subset of unfavorable cytogenetic prognosticators. Although complex karyotype (≥3 clonal cytogenetic abnormalities) and either monosomy 5 or monosomy 7 are categorized as high-risk/unfavorable cytogenetics, the presence of a monosomal karyotype was found to confer further negative prognostic influence within the high-risk group. This high-risk subgroup was first identified in a joint study conducted by the Dutch-Belgian-Swiss cooperative groups (HOVON/SAKK), which evaluated the correlation between cytogenetics and OS outcomes in patients aged 60 years or younger with AML (n = 1975). The 4-year OS rate in patients with monosomal karyotype was 4% compared with 26% in those with complex karyotype (but without monosomal karyotype).[33]

These findings were confirmed in subsequent analyses from other large cooperative group studies. In an analysis of data from patients treated on SWOG protocols (n = 1344; age 16–88 years), 13% of patients were found to have monosomal karyotype; nearly all of these cases (98%) occurred within the unfavorable cytogenetics category.[34] The incidence of monosomal karyotype increased with age, from 4% in patients 30 years of age or younger to 20% in patients >60 years of age. Among patients with unfavorable cytogenetics, the 4-year OS rate in the setting of monosomal karyotype was 3% compared with 13% without monosomal karyotype. In the setting of monosomy 7, monosomal karyotype did not appear to influence outcomes (4-year OS, 0%–3%); the 4-year OS rates in the setting of inv(3)/t(3;3) and t(6;9) and without monosomal karyotype were 0% and 9%, respectively.[34] In a retrospective study that evaluated the prognostic impact of monosomal karyotype in patients >60 years of age (n = 186) with unfavorable cytogenetics treated in a GOELAMS trial, the 2-year OS rate was significantly decreased in the setting of monosomal karyotype (7% vs. 22% without this abnormality; $P < .0001$). Similar outcomes were observed in the setting of complex karyotype.[35]

These studies show that monosomal karyotype, independent of other unfavorable cytogenetic factors, confers very poor prognosis. In the NCCN Guidelines, the presence of monosomal karyotype is included in the unfavorable-risk category of AML based on cytogenetics (see *Risk Stratification by Genetics in Non-APL AML* in the algorithm).

### Molecular Markers and Risk Stratification

The intermediate-risk cytogenetic category is the most heterogeneous group in AML, because it encompasses both normal karyotype AML (NK-AML) without gross structural abnormalities and those with structural changes that are considered neither poor risk nor favorable. Based on retrospective analyses of data from large cooperative group studies, 40% to 50% of patients with de novo AML have normal karyotype, which is

associated with intermediate risk as measured in terms of survival outcomes.[29,30] However, even in patients with NK-AML, clinical outcome is heterogeneous.

Identification of mutations that carry prognostic and therapeutic impact is rendering molecular profiling for all AML cases a standard part of the diagnostic workup. In addition to basic cytogenetic analysis, new molecular markers can help refine prognostics groups, particularly in patients with a normal karyotype. These markers include *NPM1*, FMS-like tyrosine kinase 3 (*FLT3*), *CEBPA*, isocitrate dehydrogenase 1 and 2 (*IDH1/2),* DNA (cytosine-5)-methyltransferase 3A (*DNMT3A*), and *KIT*, *TP53*, *RUNX1*, and *ASXL1* gene mutations.[36-48] Tests for these molecular markers are now available in commercial reference laboratories and in referral centers. Therefore, it is important for physicians to confer with the local pathologist on how to optimize sample collection from the time of diagnosis for subsequent molecular diagnostic tests. Testing for additional mutations may also be recommended.

***NPM1* Mutations**

The *NPM1* gene encodes a shuttle protein within the nucleolus of cells. Mutations in this gene occur in 28% to 35% of AML cases.[46,49,50] The *NPM1* mutation has been shown to be associated with NK-AML with a reported frequency of 48% to 53%.[38,44,51] Isolated *NPM1* mutation, which localizes to the cytoplasm, confers a higher complete response (CR) rate and improved event-free survival (EFS) and OS compared with NK-AML and wild-type *NPM1*, resulting in outcomes similar to cases with favorable cytogenetics (eg, CBF AML).[38,39,44,46,47]

***FLT3* Mutations**

The *FLT3* gene encodes a receptor tyrosine kinase involved in hematopoiesis. Two major classes of activating *FLT3* mutations have been identified in cases of AML, which include the internal tandem duplications (ITD) and tyrosine kinase domain (TKD) point mutations.[52-57] *FLT3*-ITD mutations occur in approximately 30% of cases and are more common than *FLT3*-TKD mutations, which occur in approximately 10% of cases.[36,40,51,56-60] Numerous studies have shown the negative prognostic influence of *FLT3*-ITD in patients with AML, resulting in shorter remission durations (eg, decreased disease-free survival [DFS] in patients who achieve a CR) and poorer survival outcomes compared with wild-type *FLT3*.[36,40,53,54,56,58,59,61] In the setting of *FLT3*-ITD and NK-AML, median OS from the time of diagnosis ranged from 6 to 12 months.[36,40,56,59]

Interestingly, a study in patients with NK-AML showed that prognosis was worse in the setting of *FLT3*-ITD without wild-type *FLT3*, compared with *FLT3*-ITD with wild-type *FLT3* in the second allele. The median OS in the setting of *FLT3*-ITD in the absence of a wild-type *FLT3* was only 7 months compared with 46 months in the setting of wild-type *FLT3* with or without *FLT3*-ITD.[56] The *FLT3*-TKD mutations predominantly occur independently of *FLT3*-ITD, and most frequently involve mutations in the D835 residue of a TKD. Although the presence of *FLT3*-TKD mutations has been shown to be associated with shorter remission durations (eg, decreased DFS) and decreased OS outcomes in some studies,[40,53,57,60] other studies have reported no impact of *FLT3*-TKD on prognosis[51,61,62] or even a favorable outcome on OS with *FLT3*-TKD mutations.[63] In the latter study from the UK MRC, the 5-year OS rates in the setting of *FLT3*-TKD mutations were 53% versus 37% without *FLT3*-TKD mutations, respectively. The 5-year OS rate was significantly higher in the setting of a higher level of *FLT3*-TKD mutations (>25%) compared with lower levels of mutations, in which OS rate was similar to cases without *FLT3*-TKD mutations (71% vs. 37%; adjusted $P$ = .004).[63]

The discrepant findings from these studies may be a result of important differences such as patient baseline characteristics, presence of concurrent genetic lesions (eg, *NPM1, CEBPA* mutations), or inclusion of the APL subtypes. Studies have shown that *FLT3*-TKD mutations can

occur in the setting of prognostically favorable *NPM1* or *CEBPA* mutations.[51,62] Moreover, *FLT3*-TKD mutations as the sole genetic aberration or occurring concurrently with t(15;17)/promyelocytic leukemia (PML)-retinoic acid receptor alpha (RARA) (underlying lesion in the APL subtype) or with *FLT3*-ITD (*FLT3* double mutation) have been associated with poorer outcomes.[51,62]

***CEBPA Mutations***

Another mutation associated with prognosis is the *CEBPA* gene, a transcription factor that plays a key role in the differentiation of granulocytes.[42] Mutations in *CEBPA* have been reported in 7% to 11% of cases of AML (or 13%–15% of cases of NK-AML) and have been associated with a favorable outcome (similar to cases of CBF translocations) with regard to increased remission duration and OS outcome compared with wild-type *CEBPA*.[41,50,51,64-66] One caveat identified was that the OS benefit with *CEBPA* was observed in the setting of double mutations of *CEBPA* but not in the setting of a single mutation of the gene. The 8-year OS rates reported in this study in the setting of double-mutant-positive, single-mutation, and wild-type *CEBPA* genes were 54%, 31%, and 34%, respectively.[65] The revised 2016 WHO classification of AML has redefined mutated *CEBPA* to indicate that biallelic (double) mutations (and not single *CEBPA* mutations) are associated with improved prognosis.[67]

***IDH1/2 Mutations***

Mutations in *IDH1* have been reported in 6% to 9% of AML cases, with a higher frequency among patients with NK-AML (8%–16%).[50,68-73] *IDH1* mutations were found to occur concurrently with NK-AML and *NPM1* mutations.[68-71,73] Additionally, these mutations have been associated with wild-type *CEBPA* and the absence of *FLT3* abnormalities.[71] Findings from published reports on the prognostic effects of *IDH1* mutations have been inconsistent. Although some studies showed no prognostic effect of *IDH1* mutations on OS when considering all *IDH* mutations (*IDH1* and *IDH2* combined) or in the overall patient population,[68-71] *IDH1* mutations correlated with significantly worse outcomes in the subgroup of patients with NK-AML with favorable- or intermediate-risk disease.[68,71,73] In the subgroup of patients younger than 60 years with favorable-risk AML (*NPM1* mutation without *FLT3*-ITD), *IDH1* mutations were associated with a significantly decreased 5-year DFS rate (42% vs. 59%; *P* = .046) and a trend for decreased OS rate (50% vs. 63%) compared with the setting of wild-type *IDH*.[71] In another study, *IDH* mutations (*IDH1* and *IDH2* combined) were associated with significantly inferior 5-year RFS rates (37% vs. 67%; *P* = .02) and OS rates (41% vs. 65%; *P* = .03) in the subgroup of patients with favorable-risk AML (NK-AML with *NPM1* mutation without *FLT3*-ITD).[73] This prognostic significance was observed when *IDH1* and *IDH2* mutations were separately analyzed, although patient numbers were small for each subgroup and statistical significance was reached only for the RFS analysis.[73] *IDH1* mutations were also associated with worse EFS and OS outcomes among the subgroup of patients with intermediate-risk NK-AML (wild-type *NPM1* without *FLT3*-ITD).[68] Mutations in *IDH2* have been reported in 8% to 12% of cases of AML,[50,68,69,73,74] with a higher frequency of 19% among those with NK-AML.[71] The presence of *IDH2* mutations was mutually exclusive with *IDH1* mutation in nearly all cases.[68,69,71] Mutations have been identified in R172 and R140 of the *IDH2* gene, with the R140 mutation occurring more frequently.[71,73,74] Interestingly, the *IDH2*-R172 mutation seemed to be mutually exclusive with *NPM1* mutations and *FLT3*-ITD.[71,73,74]

Reports on the prognostic effect of *IDH2* mutations have also been inconsistent. Some studies have reported the lack of prognostic value of *IDH2* mutations,[68,69,73] whereas others have reported favorable outcomes with *IDH2* mutations.[50,74] In one study, an association was found between *IDH2* mutations and poorer prognosis in the subgroup of patients with NK-AML and otherwise favorable risk (*NPM1* mutation without

*FLT3*-ITD).[73] However, in another study, the *IDH2* mutation (restricted to *IDH2*-R140) was associated with improved survival among the overall study population, and among the subgroup of patients with favorable risk (intermediate-risk AML with *NPM1* mutation without *FLT3*-ITD).[50] In this latter subgroup, the presence of *IDH1* or *IDH2* mutations was associated with a significantly increased 3-year OS rate compared to the setting of *NPM1* mutation without *FLT3*-ITD and without *IDH1* or *IDH2* mutations (89% vs. 31%; *P* < .0001). These results seem to suggest that in patients with NK-AML without *FLT3*-ITD, *NPM1* mutations confer a survival benefit only in the presence of concurrent *IDH* mutations.[50] The conflicting findings from the above studies require further investigation.

***DNMT3A Mutations***

The *DNMT3A* mutations have been reported in 18% to 22% of cases of AML,[50,75,76] with a frequency of 29% to 34% in cases of NK-AML.[77-79] R882 is the most commonly mutated residue. This mutation has also been observed in conjunction with *NPM1* mutations and *FLT3* mutations.[76,78,79] Data concerning the prognostic significance of *DNMT3A* mutations have thus far been conflicting. Some studies in the overall AML population and in patients with intermediate risk reported no significant effect of *DNMT3A* mutations on survival outcomes,[50,78] whereas other studies have shown a negative prognostic effect in the overall population or specific subgroups.[75-77,79] Studies have shown significantly decreased OS outcomes in the setting of *DNMT3A* mutations compared with the wild-type gene (median OS, 12–21 months vs. 40–41 months).[75,76] Significantly decreased OS with *DNMT3A* mutations has also been reported in the subgroup of patients with NK-AML with wild-type *NPM1* with or without *FLT3*-ITD, or *NPM1* mutation in the presence of *FLT3*-ITD, but not in the favorable subgroup with *NPM1* mutation without *FLT3*-ITD.[76] A study reported that in younger patients (age <60 years) with NK-AML, the presence of *DNMT3A* mutations was associated with significantly decreased OS compared with the wild-type gene (5-year OS rate, 23% vs. 45%; *P* = .02).[79] Another study also showed that in younger patients (age <60 years) with NK-AML, a *DNMT3A* mutation was associated with significantly decreased DFS (3-year rate, 20% vs. 49%; *P* = .007) and a trend toward decreased OS.[77] In this latter study, non-R882 *DNMT3A* mutations were significantly associated with poorer outcomes in patients younger than 60 years of age but not R882 mutations; in contrast, *DNMT3A*-R882 mutations (but not non-R882 mutations) in patients ≥60 years of age were associated with significantly decreased DFS (3-year rate, 3% vs. 21%; *P* = .006) and OS (3-year rate, 4% vs. 24%; *P* = .01).[77] The authors concluded that the prognostic relevance of *DNMT3A* mutations may depend on age and mutation type. Currently, the interactions of *IDH1* or *IDH2* and *DNMT3* mutations with other molecular changes require further investigation to determine the prognostic value in patients with NK-AML. Although commercial testing is available for *FLT3* and *CEBPA*, most of the other genetic mutations are not available for testing outside of the research setting. Other candidate genes that are associated with an adverse impact on outcome are *TET2* and *RUNX1*.[80,81]

***KIT Mutations***

*KIT* mutations have been reported in approximately 20% of patients with CBF AML.[43,82] Studies have shown that *KIT* mutations are associated with decreased remission duration (eg, EFS and RFS) and decreased OS in the setting of t(8;21).[37,43,45,82] However, the association of *KIT* mutations on CBF AML with inv(16) is less clear than the data for t(8;21), with several studies showing no association.[37,82,83] In an analysis from the German-Austrian AML Study Group, the frequency and prognostic impact of secondary genetic lesions were evaluated in patients with CBF AML who were treated in prospective trials (n = 176).[84] Secondary chromosomal abnormalities were found in 39% of cases, with the most common abnormalities being trisomy 22 (18%), trisomy 8 (16%), and 7q deletion (5%). Secondary genetic lesions were found in 84% of cases, including mutations in *RAS* (53%; *NRAS* in 45%; *KRAS* in 13%), *KIT*

(37%), and *FLT3* (17%; *FLT3*-TKD in 14%; *FLT3*-ITD in 5%; both mutations present in 2%). In addition, more than one of these mutations was found in 25% of cases. Mutations in *KIT* and *RAS* were less likely to occur concurrently, whereas mutations in *KIT* and *FLT3* occurred concurrently in 6% of cases.[84] Of these secondary genetic lesions, *KIT* mutation and trisomy 22 were significant independent factors predictive of RFS in multivariable analysis; *FLT3* mutations, trisomy 22, and trisomy 8 were significant independent predictors for OS.[84] These studies demonstrate the importance of secondary genetic mutations in the prognostic classification of patients with otherwise favorable-risk CBF AML (see *Risk Stratification by Genetics in Non-APL AML* in the algorithm).

***KMT2A Rearrangements***

The mixed lineage leukemia gene (*MLL*; also called *HRX*, *ALL-1*, or currently *KMT2A*), located on chromosome 11q23, was initially recognized as a recurrent locus of chromosomal translocation in AML and ALL.[85,86] In one series of 1897 AML cases, the incidence of 11q23/*KMT2A* rearrangements was 2.8%, and they were significantly higher in therapy-related AML than in *de novo* AML (9.4% vs. 2.6%, $P < .0001$).[87] The frequency of *KMT2A* rearrangements was also significantly higher among patients younger than 60 years (5.3% vs. 0.8%, $P < .0001$).[87] Depending on the fusion partner, the 11q23/ *KMT2A* rearrangement is associated with intermediate to poor prognosis.[88-90] NK-AML can be characterized by partial tandem duplication in the *KMT2A* gene (*KMT2A*-PTD),[91-93] and *KMT2A*-PTD is associated with reduced OS.[50]

***RUNX1 Mutations***

The runt-related transcription factor 1 (*RUNX1*) gene, encoding a myeloid transcription factor, is mutated in approximately 10% of *de novo* AML cases and associated with adverse prognoses.[22,94,95] In a study of adult patients with newly diagnosed AML (n = 2439), *RUNX1* mutations were associated with age ≥60 years, male gender, more immature morphology, and secondary AML evolving from MDS.[95] *RUNX1* mutations frequently co-occurred with epigenetic modifiers *ASXL1*, *IDH2*, *KMT2A*, and *EZH2*.[95] In a study examining the impact of multiple *RUNX1* mutations and loss of wild-type *RUNX1* in AML, both loss of wild-type *RUNX1* (OS, 5 months) and having ≥1 *RUNX1* mutation (14 months) had an adverse impact on prognosis compared to 1 *RUNX1* mutation (22 months; $P < .002$ and .048, respectively).[96]

***ASXL Mutations***

The *additional sex combs-like 1* (*ASXL1*) gene, located on chromosome band 20q11, encodes a protein in the enhancer of trithorax and polycomb (ETP) genes family, which have functions in transcription.[97,98] *ASXL1* mutations have been reported in approximately 5% to 36% of de novo *AML* cases,[96,99-102] and are associated with poor outcomes.[50,98,101] In an analysis of peripheral blood samples from adult patients with AML (n = 423), *ASXL1* mutations were observed to be more common in patients ≥60 years compared to patients younger than 60 years (16.2% vs. 3.2%, respectively; $P < .001$). In patients ≥60 years of age, *ASXL1* mutations were significantly associated with wild-type *NPM1*, *FLT3*-ITD mutations, mutated *CEBPA*, and lower survival.[98] A large series analyzing younger adult patients with AML (range, 18–61 years) also observed that *ASXL1* mutations were associated with older age ($P = .0001$) and decreased EFS and OS.[103] In this study, *ASXL1* mutations were also significantly associated with *RUNX1* ($P = .0001$).[103] In another study analyzing biological and prognostic subgroups based on mutations in *ASXL1, RUNX1*, *DNMT3A*, *NPM1*, *FLT3*, and *TP53* in patients with AML with myelodysplasia-related changes (n = 125), *ASXL1* (n = 26; 21%) and *TP53* (n = 28; 22%) were independently associated with shorter OS (HR, 2.53; 95% CI, 1.40–4.6; $P = .002$).[104]

***TP53 Mutations***

TP53 mutations have been reported in approximately 12%–13% of AML cases, and are associated with unfavorable risk and poor outcomes.[20,105,106] TP53 mutations are also most common in AML with

complex karyotype.[105] However, in therapy-related AML, TP53 mutations are more frequently associated with monosomal karyotype, and with abnormalities in chromosomes 5 and 7.[105] In therapy-related AML, the frequency of TP53 mutations is approximately 23%.[22] In a large analysis of different hematologic malignancies including 858 AML cases, TP53 mutations or deletions were observed in 7% and 1%, respectively, of the AML cases, and both TP53 mutations and deletions were observed in 5% of the cases.[106] TP53 mutations were significantly more frequently seen in patients ≥60 years of age when compared to patients <60 years of age (9% vs. 2%, P < .001).[106] Interestingly, compared to TP53 deletions, TP53 mutations negatively impacted survival in AML (36 months vs. 9 months, respectively; P < .001), suggesting the importance of evaluating both TP53 mutation and deletion status.[106]

***Classification and Prognostic Relevance of Gene Mutations***

The NCCN AML Panel adopted the 2017 European LeukemiaNet (ELN) recommendations for risk stratification.[21] Therefore, both NCCN and the ELN classify patients with NK-AML and mutated *NPM1* or *CEBPA* (without *FLT3*-ITD) as having favorable risk.[21,107] Specifically, patients with NK-AML with mutated *NPM1* (without *FLT3*-ITD or with a low allelic ratio [<0.5] of *FLT3*-ITD [*FLT3*-ITD$^{low}$]) or with isolated biallelic *CEBPA* mutation are categorized as having favorable risk[21] (see *Risk Stratification by Genetics in Non-APL AML* in the algorithm). In the previous ELN guidelines, a distinction was made between intermediate I and intermediate II risk groups.[108] An analysis that evaluated the prognostic value of the ELN risk classification (based on data from the German AML96 study) showed that for patients aged 60 years and younger, median RFS was shorter for the Intermediate I than for the Intermediate II group (7.9 vs. 39.1 months, respectively). In patients >60 years, no major difference was observed (9.6 vs. 11.6 months, respectively).[107] In this analysis, median OS between the Intermediate I and Intermediate II groups was not as widely separated among patients aged 60 years and younger (13.6 vs. 18.7 months, respectively); in patients >60 years, median OS was similar between the two intermediate groups (9.5 vs. 9.2 months, respectively).[107]

In another study, patients in the intermediate I group who were younger than 60 years of age demonstrated longer OS than those in the intermediate II group; in patients >60 years of age, the OS was similar between the two intermediate groups.[109] Based on these data, the ELN simplified the intermediate risk group in the 2017 update.[21] Both NCCN and the ELN classify patients with NK-AML with both mutated *NPM1* and a high allelic ratio (≥0.5) of *FLT3*-ITD (*FLT3*-ITD$^{high}$), and those with wild-type *NPM1* without *FLT3*-ITD or with *FLT3*-ITD$^{low}$ (without adverse-risk genetic lesions) as having intermediate-risk AML. In addition, t(9;11)(p21.3;q23.3), *MLLT3-MLL*, and other cytogenetic abnormalities that fall into neither the favorable nor adverse category are considered intermediate-risk. Both NCCN and the ELN classify wild-type *NPM1* and *FLT3*-ITD$^{high}$, mutated *TP53*, mutated *RUNX1*, or mutated *ASXL1* as poor risk.[21,107] However, mutated *RUNX1* or *ASXL1* should not be used as poor-risk prognostic markers if they co-occur with favorable-risk AML subtypes. (see *Risk Stratification by Genetics in Non-APL AML* in the algorithm).

As seen from the earlier discussions, patients with NK-AML may present with multiple molecular abnormalities. *NPM1* mutations can occur concurrently with *FLT3*-ITD, and outcomes in the setting of both genetic lesions are similar to isolated *FLT3*-ITD mutations.[38,44] Thus, *NPM1* mutation confers favorable prognosis only in the absence of *FLT3*-ITD.[51] Similarly, the benefit in OS outcomes seen with *CEBPA* mutations seems to be lost in the presence of concurrent *FLT3*-ITD.[65] As previously mentioned, studies suggest that *FLT3*-TKD in the presence of *FLT3*-ITD is associated with poorer prognosis. In contrast, *FLT3*-TKD may be associated with an additional favorable prognosis in the presence of

*NPM1* or *CEBPA* mutations.[62] A systematic review and meta-analysis in patients younger than 60 years of age with NK-AML further established the prognostic role of these markers.[48] OS and RFS predicted unfavorable prognosis for *FLT3*-ITD (HR, 1.86 and 1.75, respectively) and favorable prognosis for *NPM1* (HR, 0.56 and 0.37, respectively) and *CEBPA* (HR, 0.56 and 0.42, respectively).

The clinical significance of *FLT3* mutations in patients with APL remains controversial. *FLT3*-ITD is associated with a higher incidence of several hematologic features associated with APL (eg, higher WBC count, decreased fibrinogen levels, higher Sanz risk score).[110,111] However, there remains a paucity of data to support a correlation of *FLT3*-ITD on OS and rate of relapse.[110,112,113] Although mutation status alone may not reflect outcome, there was a trend for decreased OS and EFS with a higher *FLT3*-ITD mutational load suggesting that further studies are necessary to elucidate the clinical significance of this mutation.[113] Conversely, *FLT3*-TKD has not been associated with the hematologic features of APL and studies do not show a correlation of *FLT3*-TKD on outcome.[110,111,113-115]

The molecular markers discussed provide prognostic information that aid risk stratification of patients with AML and may influence subsequent treatment decisions. Research into basic leukemia biology using banked samples from clinical trials may provide keys to altered cellular pathways, which may lead to new treatment options. Risk stratification incorporating molecular data along with cytogenetics is summarized in the guidelines (see *Risk Stratification by Genetics in Non-APL AML* in the algorithm). The NCCN AML Panel recognizes that molecular genetics is a rapidly evolving field in AML; therefore, risk stratification should be modified based on continuous evaluation of evolving research data. Again, it is important for physicians to confer with the local pathologist on how to optimize sample collection from the time of diagnosis for future molecular diagnostics in patients who have NK-AML or in other situations where molecular analysis may refine the prognostic category.

### Familial Genetic Alterations in AML

Relative to sporadic cases of AML and MDS, the prevalence of known familial acute leukemia and MDS syndromes is felt to be rare, but with increasing recognition of germline mutations associated with predisposition to developing AML/MDS, identifying these syndromes is important for optimal care of patients and their relatives.[116-119] Evaluation for an underlying familial syndrome in a patient with acute leukemia or MDS should involve a screening history, focused physical examination, and diagnostic genetic testing.[116,120] In particular, the screening evaluation should determine if the patient has a family history of hematologic malignancies (including AML, acute lymphoblastic leukemia [ALL], or aplastic leukemia) or unexplained leukopenia, anemia (eg, aplastic anemia, macrocytic anemia) and/or thrombocytopenia within 2 generations.[116,117,121,122] In addition, the Nordic Guidelines for germline predisposition to myeloid neoplasms in adults recommend that the screening evaluation should determine if the patient has signs or symptoms indicative of a hereditary condition (including Li Fraumeni syndrome) that predisposes them to developing myeloid neoplasms (eg, AML or MDS).[123]Familial AML with mutated *CEBPA* is one of the most common inherited syndromes associated with AML.[116,124,125] Several reports have noted that all individuals who carry this germline mutation developed AML between 2–59 years of age.[116,124,126,127] Other familial AML syndromes include: germline mutations in *DDX41*[116,128,129] which are relatively common, and germline mutations in *MBD4*,[130] which are rare; or syndromes with platelet abnormalities, including familial platelet disorder with mutated *RUNX1*;[116,120,131] or syndromes associated with organ system manifestations, including familial MDS/AML with mutated *GATA2*.[116,120]

Based on these emerging data, the AML panel recommends that patients with a family history of leukemia, or of other hematologic cancers or abnormalities, should be evaluated for an inherited predisposition syndrome (see *Familial Genetic Alterations in AML* in the algorithm). The panel also strongly recommends that patients with a variant allele frequency (VAF) of 40–60% of genes associated with a predisposition syndrome be referred for germline testing. However, there is no consensus on optimal management of individuals diagnosed with a familial acute leukemia or MDS syndrome, so management must be individualized.[116,120]

## Principles of Acute Myeloid Leukemia Treatment

Treatment of acute leukemia has been divided into induction chemotherapy and postremission (eg, consolidation) therapy. Although obtaining a remission is the first step in controlling the disease, it is also important for patients to emerge from the induction phase in a condition to tolerate subsequent, more intensive treatments during consolidation to achieve durable disease control. In some cases, patients who either received postremission therapy or those who did not may experience relapse, usually within 6 to 9 months. Postremission therapy is recommended for patients younger than 60 years and/or who are fit for intensive therapy. However, there are trials that by design do not include postremission treatment for patients and the results have been promising; these trials are generally in older patients with AML. The induction strategy is influenced by individual patient characteristics such as age, presence of comorbid conditions affecting performance status, and preexisting myelodysplasia. This is particularly true of patients who are older with AML. Patients whose performance status would make them poor candidates for the standard antineoplastic regimens may still be able to participate in clinical trials or low-intensity therapy plus oral agents designed to target this underserved patient population. Supportive care may also be an appropriate choice. In younger patients, strategies for consolidation are based on the potential risk of relapse, with higher-risk patients receiving more aggressive therapy. Cytogenetic and molecular abnormalities are the most significant prognostic indicators; however, failure to achieve remission after 1 cycle of induction therapy or high tumor burden, defined as a WBC count ≥40,000/mcL,[24] are included as poor-risk factors for long-term remission. Therefore, response is assessed based on bone marrow morphology and cytogenetic and molecular responses taken at several points during the course of treatment (see *Response Criteria Definitions for Acute Myeloid Leukemia* and *Monitoring During Therapy* in the algorithm for definitions of CR and partial response [PR] and disease relapse). The use of flow cytometry and/or molecular methods to assess MRD is emerging as a novel determinant to assess the depth of therapeutic response at the time of morphologic remission in patients with AML (see *Role of MRD Monitoring*).

Finally, all patients require attentive supportive care related to the underlying leukemia (ie, tumor lysis syndrome) and the adverse effects of chemotherapy (see *Supportive Care* in the algorithm).

## Management of Acute Promyelocytic Leukemia

APL is a particularly aggressive subtype of AML, comprising approximately 10% of AML cases. APL has a distinct morphology and clinical presentation that may be associated with a high early death rate due to potentially fatal coagulopathy.[132-134] In an analysis of data (from 1992–2007) from the National Cancer Institute SEER registry, the age-adjusted annual incidence rate of APL was 0.23 per 100,000 persons.[135] The median age of APL diagnosis was 44 years, which is younger than that of patients with AML (median age 67 years).[2,135] APL is cytogenetically distinguished by the t(15;17) chromosomal translocation. The translocation of the *PML* gene on chromosome 15 to the *RARA* gene on chromosome 17 [ie, t(15;17)(q24.1;q21.1)] produces a *PML-RARA* fusion gene that can be quantitatively monitored using polymerase chain

reaction (PCR) to document disease burden and to ultimately confirm molecular remission. As further emphasis of the cytogenetic attribute of APL, the most recent WHO classification of myeloid neoplasms and acute leukemia changed the definition of APL from the cytogenetic criteria of t(15;17) to the molecular definition of "APL with PML-RARA" to be inclusive of complex or cryptic rearrangements that lead to a functional transcription factor.[67]

APL may be *de novo* or therapy-related. Some of the following attributes of therapy-related APL (t-APL) were highlighted in a systematic review: 1) the average age of diagnosis is 47 years with a higher incidence in females; 2) the risk significantly declines 2 years after completion of treatment for the primary antecedent disease; 3) breast cancer, hematologic malignancy, multiple sclerosis, and genitourinary malignancy are the most common antecedent diseases; 4) topoisomerase II inhibitors and radiation have the highest risk associated with developing t-APL; 5) the clinicopathology of t-APL is not different from de novo APL; 6) the single mutation t(15;17) is most common; and 7) the remission rate of t-APL is 80%, which is comparable to de novo APL.[136] Therefore, t-APL and de novo APL are treated similarly.

The incorporation of all-trans retinoic acid (ATRA) and the use of risk stratification (based on WBC counts) in the management of APL has largely improved outcomes for patients with this subtype. The unique ability of ATRA to produce differentiation in APL blasts can reverse the coagulopathy, which is the major cause of death during induction. To minimize early induction mortality due to coagulopathy, patients with a presumptive diagnosis of APL based on morphology, immunophenotype, and/or coagulopathy with a positive disseminated intravascular coagulation screen should promptly start ATRA. It is not necessary to wait for molecular testing or bone marrow with cytogenetics to confirm the diagnosis. The initial clinical diagnosis of APL may be confirmed by FISH or PCR ideally in the peripheral blood and if not confirmed, ATRA may be discontinued and standard AML therapy initiated.

Studies have demonstrated the necessity of early recognition and prompt initiation of ATRA based on a presumed diagnosis of APL to reduce the rate of early mortality. This is evidenced by early death rates below 10% reported for patients enrolled in clinical trials[137-141] compared to the general population where early mortality rates are still in excess of 15%.[135,142-144] Data from the SEER registry measured 2-year survival and 30-day mortality from 1977 to 2007 and found a 61% improvement in 3-year survival per decade ($P$ = .001) but a consistent rate of 30-day mortality averaging 20%.[142] Education of heath care providers to identify the first suspicion of APL may extend the improved outcomes seen in clinical trials to the general population if treatment is not delayed.

There is a high frequency of *FLT3* mutations in APL. In a systematic review including 11 studies, *FLT3*-ITD frequency in APL occurred in about 12% to 38% of cases and *FLT3*-TKD occurred in 2% to 20% of cases.[145] Data are inconsistent about whether *FLT3*-ITD in APL results in a negative prognosis. Several studies support this association and further correlate *FLT3*-ITD with higher WBC counts, lower platelet counts, and the expression of the bcr3 PML-RARA fusion transcript.[145-148] However, data from other studies have not shown a correlation.[58,149] It has been proposed that the discrepancy between studies may be at least partially resolved by incorporation of a *FLT3*-ITD/wild-type ratio to measure the effect on prognosis.[113,150] Data showed that a ratio of greater than 0.66 resulted in a shorter 5-year RFS.[150] Similarly, shorter EFS and OS were observed in the setting of equal to or greater than a 0.5 ratio compared to less than 0.5 (EFS, $P$ = .029; OS, $P$ = .084).[113] While data may correlate with prognosis, there currently remains no change in treatment course depending on expression of *FLT3*-ITD.

### Induction Therapy for Patients with APL

The evolution of treatment strategies for APL, built on clinical observation and well-constructed clinical trials, represents one of the most rewarding sagas of modern hematology. An early study by a group in Shanghai reported a CR rate of 85% in response to single-agent ATRA.[151] The first North American Intergroup study confirmed a 70% CR rate with single-agent ATRA, which was equivalent to rates obtained with conventional doses of cytarabine and daunorubicin.[152,153] Induction regimens with ATRA combined with anthracyclines (with or without cytarabine) are associated with CR rates exceeding 90%, as demonstrated in several large cooperative group trials.[154-157] Using ATRA-based induction regimens followed by consolidation with regimens containing either ATRA with anthracyclines, or cytarabine with anthracyclines, more than 80% of patients with APL can be cured of their disease.[154,156-158] ATRA with arsenic trioxide (ATO) has resulted in improved outcomes for patients with APL.[159] Risk stratification is a major consideration in the treatment of APL (see *APL: Classification and Treatment Recommendation* in the algorithm).[157] Although clinical trials may group patients into those with low-, intermediate-, or high-risk disease, the NCCN Panel categorizes patients with APL as having low-risk disease (WBC count ≤10,000/mcL) or high-risk disease (WBC count >10,000/mcL). Patients with low-risk disease are typically treated with less intensive consolidation regimens compared with regimens used for patients with high-risk disease.

The French APL 93 trial compared sequential therapy of ATRA followed by chemotherapy (cytarabine and daunorubicin) with concurrent ATRA plus chemotherapy. CR rates were 92% in both arms, but the relapse rate at 2 years was 6% in the combined ATRA plus chemotherapy group versus 16% for the sequential group.[138,160] Induction regimens were pared down to ATRA and idarubicin (the AIDA schedule) in both the Italian GIMEMA 93 trial and the Spanish PETHEMA LPA 94 trial, which produced CR rates of 89% to 95%, raising the question of whether there was a need for cytarabine in APL induction.[137,141] In these trials, 51% to 61% of evaluable patients achieved PCR-negative status for *PML-RARA* following induction therapy; 93% to 98% achieved PCR-negative status after consolidation. The estimated 2-year EFS rate was 79% in both trials.[137,141] In the PETHEMA trial, the 2-year OS rate was 82%.[141]

Following observational data that correlated elevated WBC counts and high-risk disease (based on both the higher number of deaths during induction and the increased rates of relapse), in the PETHEMA LPA 94 trials, Sanz et al[161,162] devised a risk stratification study based solely on WBC and platelet counts at presentation. In this study, the induction regimen remained the same (AIDA), but ATRA was added to consolidation cycles 1 to 3 for all but patients with low-risk disease (ie, WBC ≤10,000/mcL and platelets >40,000/mcL). The CR rate in this trial was 90% with almost all the failure attributed to hemorrhage, infection, or differentiation syndrome. Factors predictive of death during induction were a WBC count greater than 10,000/mcL, age >60 years, creatinine of 1.4 or greater, and male gender.[161,162] In 2006, Ades et al[163] reported the outcome of the French APL 2000 trial (n = 340) in which patients younger than 60 years of age with WBC counts less than 10,000/mcL were randomized to receive ATRA (45 mg/m$^2$) and daunorubicin (60 mg/m$^2$/day for 3 days) as induction therapy with or without cytarabine (200 mg/m$^2$/day for 7 days). Those randomized to cytarabine for induction also received cytarabine during consolidation.[163] Patients with WBC counts greater than 10,000/mcL or age >60 years received cytarabine. While the CR rates were similar between the randomized groups (99% with cytarabine and 94% without cytarabine), those receiving cytarabine had a lower 2-year cumulative incidence of relapse (5% with cytarabine and 16% without cytarabine) that translated into an improved EFS rate (93% with cytarabine and 77% with no cytarabine) at 2 years. The 2-year OS rate was 98% with cytarabine and 90% without cytarabine. Among patients with a WBC count

greater than 10,000/mcL, the CR rate was 97%; the 2-year EFS rate was 89% for those younger than 60 years of age and 79% for those >60 years of age.[163] A report of a joint analysis of the outcomes in the PETHEMA 99 and the French APL 2000 trials in patients younger than 65 years of age showed that in patients with a WBC count less than 10,000/mcL, CR rates were similar, but the relapse rates at 3 years were lower in the PETHEMA trial, which used AIDA and no cytarabine during induction (with ATRA during consolidation), than in the APL 2000 cytarabine-containing regimen (4% vs. 14%; *P* = .03).[155] However, for patients with a WBC count greater than 10,000/mcL, the cytarabine-containing protocol resulted in higher CR (95% vs. 84%; *P* = .018) and 3-year OS rates (91.5% vs. 81%; *P* = .026).[155] The second North American Intergroup trial also used ATRA (45 mg/m$^2$), daunorubicin (50 mg/m$^2$/day for 4 days), and cytarabine (200 mg/m$^2$/day for 7 days) with a similar initial CR rate of 90%.[156] Consolidation in this trial differed in that two cycles of ATO were given following induction and prior to the final two cycles of anthracycline.

ATO has been found to be a potent promoter of apoptosis in APL cells.[164,165] In 2004, Shen et al[166] first published outcomes using single-agent ATRA, single-agent ATO, or the combination of both drugs.[166] While CR rates exceeded 90% in all three treatment arms, the decline in quantity of PML/RARA fusion transcripts (as measured by quantitative PCR) was significantly higher with the combination. Time to hematologic response was more rapid and RFS (after a median follow-up of 18 months) was improved with the combination regimen compared with the monotherapy regimens.[166] Subsequently, Estey et al[167] used a similar combination of ATRA and ATO to treat patients with low-risk APL.[167] Patients with high-risk APL in the same study were treated with ATRA and ATO combined with gemtuzumab ozogamicin (GO; 9 mg/m$^2$ on day 1 of induction therapy). In a report from this study (n = 82), the CR rate in all patients was 92% (95% for patients with low-risk APL and 81% for patients with high-risk APL) and the estimated 3-year OS rate was 85%.[168] The authors suggested that ATRA combined with ATO, with or without GO, may be an alternative to conventional chemotherapy in patients with untreated APL. A subsequent study examined the long-term outcomes of patients with newly diagnosed APL treated with ATRA and ATO with or without GO [9 mg/m$^2$ on day 1 of induction therapy for high-risk APL patients] (n = 187; median age, 50 years; range, 18–84 years).[169] The complete remission rate was 96% for patients with both low- and high-risk APL. With a median follow-up of 47.6 months (range, 2.7–159.7 months), the 5-year EFS, DFS, and OS rates for patients with low-risk APL were 87%, 99%, and 89%, respectively, and for patients with high-risk APL were 81%, 89%, and 86%, respectively.[169] These data suggested that ATRA and ATO combined with GO is feasible and elicits durable responses. In another study by Estey et al,[170] patients with APL were treated with ATRA and GO (9 mg/m$^2$ on day 1 or 5 of induction therapy). Patients with WBC counts of >30,000/mcL also received idarubicin (12 mg/m$^2$/day on days 1–3). In this study (n = 19), the CR rate in all patients who received ATRA plus GO and idarubicin was 84%, and 88% in patients who received ATRA plus GO.[170] However, clinicians should be aware of possible adverse events associated with GO including sinusoidal obstruction syndrome similar to hepatic veno-occlusive disease described in the transplant setting.[171,172]

A phase II study (APML4) from Australia/New Zealand evaluated an induction regimen with ATO added to a backbone of AIDA in patients with previously untreated APL (n = 124; median age, 44 years).[173] Patients received 1 cycle of induction therapy with ATRA (45 mg/m$^2$ days 1–36 in divided doses), age-adjusted idarubicin (6–12 mg/m$^2$ days 2, 4, 6, and 8), and ATO (0.15 mg/kg days 9–36 as a 2-hour IV infusion). All patients received prednisone (1 mg/kg/day for at least 10 days) regardless of initial WBC count as prophylaxis for differentiation syndrome.[173] The most common grade 3 or 4 non-hematologic adverse events during induction included infections (76%; including febrile neutropenia), hepatic toxicity

(44%), gastrointestinal toxicity (28%), metabolic abnormalities (16%), and prolonged QTc interval (14%); grade 3 or 4 differentiation syndrome occurred in 14% of patients. Patients who achieved CR following induction received consolidation with 2 cycles of ATRA and ATO. Maintenance therapy was administered for 2 years and consisted of eight 3-month cycles of treatment with ATRA, oral methotrexate, and 6-mercaptopurine.[173] Grade 3 or 4 adverse events occurred primarily during induction (as above); the most common grade 3 or 4 events during consolidation (cycle 1) included infections (19%) and hepatic toxicity (12%), and no deaths occurred during consolidation cycles. The hematologic CR rate after induction was 95%; early death (during induction) occurred in 3% of patients. The 2-year DFS and failure-free survival rates were 97.5% and 88%, respectively. The 2-year OS rate was 93%.[173] This trial enrolled 24 patients that were defined as having high risk disease based on the Sanz criteria. OS was not affected by the Sanz risk group ($P_{[trend]}$ = .17), although a correlation was made with the failure-free survival rate ($P_{[trend]}$ = .03). This association may be attributed to the method of analysis that included patients who withdrew from the study due to denial of treatment or excessive toxicity, as well as patients who experienced relapse, death, or failure to achieve a molecular CR.

In a phase III randomized trial of the Italian-German Cooperative Group, induction with ATRA combined with ATO was compared with the AIDA regimen in patients with newly diagnosed, low-, or intermediate-risk APL (n = 162; APL0406 study).[159] Patients in Arm A received ATRA (45 mg/m$^2$) plus ATO (0.15 mg/kg) daily until CR, then ATO 5 days per week for 4 weeks every 8 weeks for a total of 4 courses, and ATRA daily for 2 weeks every 4 weeks for a total of 7 courses. Patients in Arm B received standard AIDA induction followed by consolidation with 3 cycles of anthracycline-based consolidation combined with ATRA and then maintenance comprising low-dose chemotherapy and ATRA.[158] In addition, all patients received prednisone (0.5 mg/kg/day from day 1 until the end of induction) as prophylaxis for differentiation syndrome. The primary endpoint of this study was the 2-year EFS rate. Among evaluable patients (n = 156), CR rates were not different between Arm A and Arm B (100% vs. 95%). After a median follow-up period of 34.4 months, the 2-year EFS rate was significantly higher in Arm A compared with Arm B (97% vs. 86%; $P$ < .001 for non-inferiority; $P$ = .02 for superiority). The 2-year OS probability was also significantly higher in Arm A compared with Arm B (99% vs. 91%; $P$ = .02). Four patients in Arm B died during induction therapy (2 deaths were caused by differentiation syndrome). One patient in Arm A and 3 patients in Arm B died during consolidation. Grade 3 or 4 neutropenia and thrombocytopenia lasting more than 15 days were significantly more frequent in Arm B compared with Arm A throughout induction and consolidation cycles. Grade 3 or 4 hepatic toxicities also occurred more frequently in Arm A compared with Arm B (63% vs. 6%; $P$ < .001).[159] Health-related quality-of-life outcomes were not significantly different between treatment groups except for fatigue severity. There was improvement in fatigue following induction in the ATRA plus ATO group ($P$ = .022), though the benefit was negligible by third consolidation ($P$ = .660).[174] This randomized study showed non-inferiority of an ATRA plus ATO regimen compared with AIDA, which may allow for elimination of chemotherapy agents in the initial treatment of patients with non–high-risk APL.

Data from the randomized phase III AML17 trial compared ATRA plus ATO to AIDA in a cohort of 235 patients. ATRA was given to both groups in daily divided oral doses (45 mg/m$^2$) until remission or until day 60, after which patients were treated 2 weeks on then 2 weeks off.[175] The AIDA group received four cycles of consolidation consisting of 12 mg/m$^2$ IV idarubicin on days 2, 4, 6, and 8 in the first course; 5 mg/m$^2$ IV idarubicin on days 1 through 4 in course 2; 10 mg/m$^2$ mitoxantrone on days 1 through 4 in course 3; and 12 mg/m$^2$ idarubicin on day 1 of the final course.[175] The ATRA plus ATO treatment entailed 0.3 mg/kg IV ATO on

days 1 through 5 in the first week and 0.25 mg/kg twice weekly in weeks 2 through 8 in course 1 and then twice weekly in weeks 2 through 4 during courses 2 through 5. Patients with high-risk disease could receive an initial dose of GO (6 mg/m$^2$ IV). Comparison between the ATRA plus ATO group and the AIDA group showed a higher 4-year EFS (91% vs. 70%; *P* = .002) and lower 4-year cumulative incidence of morphologic relapse (1% vs. 18%; *P* = .0007) for ATRA plus ATO compared to AIDA, though no statistically significant difference in 4-year survival was seen (93% vs. 89%; *P* = .25). Quality of life was equivalent in the treatment groups for both patients with high- and low-risk disease as measured by the primary outcome of global functioning (effect size, 2.17; 95% CI, -2.79–7.12; *P* = .39).[175] However, the data from the trial measured more supportive care treatments and higher liver toxicity with AIDA. Treatment schedule differed from previous trials by moving to a higher dose of ATO given at a lower frequency of twice weekly. Though data are limited to this single trial, the NCCN AML Panel recognizes that this alternative dosing schedule may be more manageable for patients who have difficulty getting to the clinic.

All five induction regimens discussed above offer excellent outcomes. These regimens are ATRA plus ATO (0.15 mg/kg; with the addition of idarubicin for patients with high-risk disease only); ATRA plus daunorubicin (50 mg/m$^2$ daily for 4 days) plus cytarabine; ATRA plus daunorubicin (60 mg/m$^2$ daily for 3 days) plus cytarabine; AIDA; or ATRA plus ATO (0.3 mg/kg). Choice of regimen will be influenced by risk group, age, and cardiovascular risks. The NCCN AML Panel recommends that patients with APL be treated according to one of the regimens established from the clinical trials; importantly, one should use a regimen consistently through all components of the protocol and not mix induction regimens from one trial with consolidation regimens from another trial. With the advances in treatment regimens, the panel emphasizes the importance of receiving treatment from an established treatment center for the monitoring and treatment of adverse events, regardless of risk stratification. The recommendations within the guidelines are broken down by: 1) risk classification using WBC count (cutoff of 10,000/mcL) at diagnosis; and 2) whether patients with high-risk disease have cardiac issues.

For patients with low-risk disease (WBC counts ≤10,000/mcL), for initial induction the panel recommends ATRA plus ATO (0.15 mg/kg)[159] (category 1, preferred regimen); and ATRA plus ATO (0.3 mg/kg)[175] (category 1, preferred regimen). If arsenic is contraindicated or not available, the panel recommends AIDA[157] (category 1); ATRA plus a single dose of GO (9 mg/m$^2$ on day 5)[170]; or enrollment in a clinical trial.

For patients with high-risk disease (WBC counts >10,000/mcL), the NCCN AML Panel historically recommended a regimen that included cytarabine along with ATRA plus daunorubicin (PETHEMA LPA 99 trial) over AIDA (APL 2000 trial) because of higher CR and 3-year OS rates.[155,157] To improve patient outcome, the PETHEMA LPA 99 trial and the GIMEMA AIDA-0493 study were modified to incorporate the combination of ATRA with cytarabine either during induction (LPA 2005)[157] or during consolidation (AIDA-2000).[158] The improved outcomes in both of these studies suggest a supra-additive effect with ATRA plus cytarabine, independent of the anthracycline. The APML4 trial has shown the benefit of induction that includes ATRA and ATO. Unlike the other regimens, the APML4 trial does not use cytarabine during induction. In light of these studies, the panel recommends initial induction with these preferred regimens: ATRA and ATO,[173] or ATRA and ATO with a single dose of GO (9 mg/m$^2$[169] or 6 mg/m$^2$[175] that may be given on day 1, day 2, day 3, or day 4). Other recommended regimens include ATRA plus daunorubicin and cytarabine[153,155,156]; AIDA alone[157]; or enrollment in a clinical trial. In patients with high-risk disease with cardiac issues that include low ejection fraction, the panel recommends initial induction with ATRA and ATO with a

single dose of GO (9 mg/m$^2$ on day 1[169] or 6 mg/m$^2$ on day 1[175]). If the patient with high-risk disease exhibits signs of prolonged QTc, the panel recommends initial induction with ATRA and a single dose of GO (9 mg/m$^2$ on day 1)[170]; ATRA plus daunorubicin and cytarabine[153,155]; or AIDA alone.[157]

The sudden onset of differentiation syndrome and the severity of the complications have resulted in the frequent use of preemptive dexamethasone, because there are no markers to predict its development. The panel recommends the prophylactic administration of corticosteroids in patients with a WBC count greater than 10,000/mcL (or in patients receiving induction with both ATRA and ATO, regardless of WBC count) to prevent differentiation syndrome. The ATRA plus ATO regimens defined by Lo-Coco et al[159] or Iland et al[173,176] use prednisone 0.5 mg/kg as prophylaxis for differentiation syndrome but with differing durations and tapering schedules. For patients who develop differentiation syndrome on these regimens despite prednisone prophylaxis, prednisone should be stopped and replaced with dexamethasone 10 mg twice daily (see *Supportive Care for APL* in the algorithm). If using non-ATO regimens, either steroid regimen is acceptable although there may be a slight preference for dexamethasone for high-risk disease. While the panel recommends the use of prophylactic corticosteroids, it is acknowledged that corticosteroids may not be necessary in all patients. Some institutions may advocate a low threshold for initiating corticosteroids instead of defaulting to prophylaxis. Until more studies are done to address this issue, consistency to the selected protocol should be sought.

### Consolidation Therapy for Patients with APL

Because the differentiating action of ATRA occurs over a longer time period than the cytoreduction of conventional chemotherapy, early marrow evaluations for hematologic response at days 7 to 14 post induction are misleading and may lead to overtreatment. Marrow evaluation is not recommended until recovery of blood counts, usually 4 to 6 weeks after induction. Cytogenetic analysis is usually normal by this point, but molecular remission often requires at least 2 cycles of consolidation. Thus, the first assessment of molecular remission should not be performed prior to count recovery. At count recovery following induction therapy, patients should proceed with consolidation. For patients with low-risk disease, if a patient is cytopenic on days 28–35, bone marrow biopsy and aspirate is recommended to document blast clearance and to assess whether the marrow is suppressed and to determine whether ATRA and ATO should be held to allow count recovery. If, however, blood counts have recovered by this time point, a bone marrow biopsy may be considered to document remission but is optional. For patients with high-risk disease, LP should be considered at count recovery following induction therapy, before proceeding with consolidation.[177] Many consolidation regimens involve high cumulative doses of cardiotoxic agents. It is therefore important to assess the cardiac function of patients prior to initiating each anthracycline- or mitoxantrone-containing consolidation cycle. Consolidation regimens employing ATO will require monitoring of the QTc interval and optimizing electrolytes (see *Supportive Care for APL* in the algorithm and *Supportive Care for Patients with APL* in the discussion). According to the package insert, for QTc greater than 450 msec for males and 460 msec for females, corrective measures should be initiated and reassessment with serial electrocardiograms (ECGs) should be performed prior to ATO treatment.[178]

The goal of consolidation therapy for APL is a durable molecular remission. Data from the two sequential PETHEMA trials,[141,161,162] which produced the current risk model, were used to construct subsequent trials that intensify therapy for the high-risk groups. In the second PETHEMA trial (LPA 99), 15 days of ATRA (45 mg/m$^2$) were added to each of three cycles of anthracycline-based consolidation therapy. Overall, relapse rates were reduced from 20% to 9% with the incorporation of ATRA in the

consolidation phase.[161] For the low-risk group, there was no difference in relapse rate (3%–6%) or in 3-year DFS rate (93%–97%) between the ATRA group compared with a similar consolidation without ATRA in the LPA 94 trial.[161] Among patients with intermediate risk disease, the relapse rate was reduced from 14% to 2.5% with the incorporation of ATRA; the 3-year DFS rate was 97% with ATRA consolidation versus 82% in historical controls.[161] Although the addition of ATRA to the high-risk group improved relapse and DFS rates, there were significant rates of relapse (26%) and 3-year DFS (77%). In the PETHEMA LPA 2005 study, both ATRA and cytarabine were included in the anthracycline-containing consolidation regimen for patients with high-risk disease.[157] In this high-risk group, the 3-year relapse rate was reduced to 11% (compared with 26% from the LPA 99 study), and the 3-year DFS and OS rates were 82% and 79%, respectively. The LPA 2005 trial also began to approach the question of how to reduce toxicity during consolidation therapy in patients with low- and intermediate-risk disease by dose reduction of mitoxantrone (from 10 mg/m$^2$/day for 5 days to 10 mg/m$^2$/day for 3 days in cycle 2) and a small reduction of idarubicin dose for low- and intermediate-risk groups (from 7 mg/m$^2$/day for 4 days to 5 mg/m$^2$/day for 4 days in cycle 1 and from 2 doses of 12 mg/m$^2$/day to 1 dose of 12 mg/m$^2$/day in cycle 3). Based on results in the low- and intermediate-risk groups, lowering the dose of mitoxantrone resulted in reduction of toxicity and hospital stay while maintaining the anti-leukemic activity (compared with results in low- and intermediate-risk groups from the LPA 99 study). With the consolidation regimens evaluated in the LPA 2005 study, outcomes were similar between low-risk and intermediate-risk groups with regard to the 3-year cumulative incidence of relapse (6% vs. 6%), the 3-year DFS (93% vs. 94%), and the 3-year OS rate (96% vs. 93%).[157]

The AIDA-2000 trial of the Italian GIMEMA group has confirmed that inclusion of ATRA in consolidation significantly improved outcome, most notably for patients with high-risk disease; the high-risk group received a consolidation regimen containing ATRA and cytarabine along with anthracyclines.[158] In this study, the 6-year cumulative incidence of relapse was 9% for patients in the high-risk group; the 6-year DFS and OS rates in this group were 84.5% and 83%, respectively. In the AIDA-2000 study, the low- and intermediate-risk groups were collapsed into a single category, and received the same consolidation regimen with ATRA, mitoxantrone, and idarubicin (ATRA 45 mg/m$^2$ for 15 days + idarubicin 5 mg/m$^2$ for 4 days in cycle 1; ATRA for 15 days and mitoxantrone 10 mg/m$^2$/day for 5 days in cycle 2; and ATRA for 15 days and idarubicin 12 mg/m$^2$ for 1 dose in cycle 3). For patients in the low- and intermediate-risk group, the 6-year cumulative incidence of relapse was 11%; the 6-year DFS and OS rates in this group were 86% and 89%, respectively.[158]

In the European APL 2000 trial, which randomized daunorubicin with or without cytarabine for the consolidation phase (no ATRA during consolidation) for the low- and intermediate-risk (ie, “standard risk”) groups, the 2-year EFS rate was higher with the addition of cytarabine.[163] Long-term follow-up from this study showed that in patients with standard risk disease, the addition of cytarabine substantially reduced cumulative incidence of relapse (7-year relapse rate 13% vs. 29%; $P$ = .0065) and increased 7-year EFS rates (83% vs. 65%; $P$ = .0029) compared with the regimen without cytarabine.[179] A poorer response was seen in patients who did not receive cytarabine despite maintenance treatment of continuous 6-mercaptopurine plus methotrexate and intermittent ATRA. Furthermore, all patients with high-risk disease received cytarabine during induction and consolidation resulting in a 7-year relapse rate, EFS rate, and OS rate of 7.1%, 82.2%, and 87.6%, respectively, an outcome that was slightly improved over patients with standard-risk disease treated without cytarabine. Although the results of the European APL 2000 trial are limited by the use of a single anthracycline in all study arms, the data support the use of cytarabine in standard-risk APL with the anthracycline daunorubicin.

The North American Intergroup trial also focused on decreasing toxicity during consolidation by incorporating ATO into the consolidation schema directly after achieving remission.[156] In this trial, patients who were randomized to receive 2 courses of 25 days of ATO (5 days a week for 5 weeks) immediately after entering CR followed by the standard post-remission regimen with 2 more courses of ATRA plus daunorubicin, had a significantly higher 3-year EFS rate (80% vs. 63%; $P < .0001$) and improved OS outcomes (3-year OS rate 86% vs. 81%; $P = .06$) compared with those who received only the 2 courses of ATRA plus chemotherapy. The 3-year DFS rate was also significantly improved with the addition of ATO (90% vs. 70%; $P < .0001$). The favorable outcomes with the incorporation of ATO were observed in patients with low-/intermediate-risk and high-risk disease.[156] Notably, in the high-risk group, DFS outcomes with the addition of ATO were similar to the DFS rate observed for the low-/intermediate-risk group, suggesting that ATO may help to overcome the negative prognostic influence of high-risk disease. The overall outcomes do not appear to be superior to the less complex consolidation schedules used in either of the two most recent European trials for patients in the low- and intermediate-risk groups, but did appear to offer improved survival for patients with high-risk disease. However, the consolidation phase in the North American Intergroup protocol is longer and may be difficult for some patients to complete.

The French APL 2006 randomized trial evaluated the role of ATO in consolidation therapy for previously untreated APL, both for patients with standard-risk disease (WBC count <10,000/mcL; ATO vs. cytarabine vs. ATRA, all in combination with idarubicin during consolidation) and patients with high-risk disease (WBC >10,000/mcL; cytarabine vs. ATO + cytarabine, both in combination with idarubicin during consolidation).[180,181] Based on results from the interim analysis (median follow-up, 22–24 months), all regimens resulted in CR rates exceeding 95% with low rates of relapse. However, the use of ATO in the consolidation phase was associated with longer durations of myelosuppression, which necessitated a protocol amendment to further reduce the chemotherapy dose in patients receiving ATO.[180] In the second interim analysis, the only change was a decrease of idarubicin during second consolidation. Data from this analysis show a 99.4% CR across all groups encompassing a total of 347 patients.[181] While the two-year EFS and OS rates were above 95% for all three groups, there was a reduction of myelosuppression in the group treated with AIDA compared to idarubicin plus cytarabine and idarubicin plus ATO, which had similar durations.[181] The potential benefits of the use of ATO or ATRA in consolidation may rest in a lower risk for long-term cardiovascular complications and a lower risk for secondary myelodysplasia.

In the phase II APML4 study from Australia/New Zealand, 2 cycles of ATO and ATRA were used as consolidation in patients who achieved a CR after a 3-drug induction with ATRA, idarubicin, and ATO.[173] Among the patients who proceeded to consolidation (n = 112), all achieved molecular remission, and the 2-year DFS rate was 97.5%. The 2-year OS rate in all evaluable patients in this study (n = 124) was 93%.[173] As discussed earlier, in the phase III randomized trial of ATRA combined with ATO versus the AIDA regimen (APL0406 study) in patients with newly diagnosed, low-, or intermediate-risk APL (n = 162), patients in the ATRA plus ATO arm received consolidation with ATO 5 days per week for 4 weeks every 8 weeks for a total of 4 courses, and ATRA daily for 2 weeks every 4 weeks for a total of 7 courses (Arm A).[159] Patients in the AIDA arm (Arm B) received 3 cycles of anthracycline-based consolidation combined with ATRA and then maintenance with low-dose chemotherapy and ATRA.[158] After a median follow-up period of 31 months, the 2-year EFS rate was significantly longer in Arm A compared with Arm B (97% vs. 86%; $P < .001$ for noninferiority; $P = .02$ for superiority of ATRA-ATO). In addition, the 2-year OS was also longer in Arm A (99% vs. 91%; $P = .02$),

with no differences in 2-year DFS (97% vs. 90%; *P* = .11) or cumulative incidence of relapse (1% vs. 6%; *P* = .24) between treatment arms.[159]

In the French APL 93 trial, a 4% incidence of CNS relapse was reported in patients with WBC counts greater than 10,000/mcL. In the APL 2000 trial, that high-risk population received five doses of IT chemotherapy using a combination of methotrexate, cytarabine, and steroids, upon count recovery following induction therapy. These patients also received a higher dose of cytarabine (2 g/m$^2$) during consolidation (in cycle 2) as compared with 1 g/m$^2$ in the APL 93 trial. There were no cases of CNS relapse in the APL 2000 trial, compared with 5 cases in the APL 93 trial. While the original treatment protocol on APL 2000 used HiDAC in the second cycle of consolidation, some investigators suggest the use of HiDAC earlier, particularly in those patients who are not receiving IT therapy for CNS prophylaxis.

For patients with low-risk disease, the NCCN AML Panel has positioned the ATRA plus ATO regimen first, based on results from the APL0406 phase III randomized trial in comparison with the AIDA regimen.[159] An additional ATRA plus ATO regimen based on the AML 17 trial[175] is also a preferred option. The GIMEMA AIDA-2000 regimen[158] is an additional option. However, all three of these regimens will yield excellent results. It is important to note that clinicians should use a regimen consistently through all components of the treatment protocol and not mix induction regimens from one trial with consolidation regimens from another trial.

For patients with high-risk disease, preferred consolidation therapies include ATRA plus ATO as used in the APML4 trial,[173] or ATRA and ATO (plus a single dose of GO if ATRA/ATO are discontinued due to toxicity).[169,175] Other recommended consolidation approaches include cytarabine with daunorubicin as used in the French APL 2000 trial[163]; cytarabine with AIDA as used in the PETHEMA LPA 2005[157]; and 2 cycles of ATO followed by 2 additional cycles of standard chemotherapy as used in the North American Intergroup trial.[156] When using a cytarabine-containing regimen, dose adjustments of cytarabine may be needed for patients who are older or for patients with renal dysfunction.[155,156] In patients who could not tolerate anthracyclines and who received ATRA and ATO for induction therapy, the reported trials continued with repeated cycles of these two agents following induction without anthracycline.[167,168] For patients with high-risk disease and cardiac issues (eg, low ejection fraction and prolonged QTc), the NCCN AML Panel recommends ATO (0.15 mg/kg or 0.3 mg/kg) with ATRA for consolidation.[169,175] If ATRA or ATO are discontinued due to toxicity, a single dose of GO (9 mg/m$^2$) may be considered once every 4 to 5 weeks until 28 weeks from CR. If the patient received ATRA and GO as induction therapy, consolidation with ATRA and GO should follow.[170] As mentioned previously, the panel suggests that a regimen should be used consistently through all components and physicians should not mix induction therapy from one trial with consolidation therapy from another.

In general, it is recommended that 4 to 6 doses of intrathecal (IT) chemotherapy be given during consolidation for patients with high-risk APL. IT chemotherapy may include agents such as methotrexate alternating with cytarabine either alone or combined with corticosteroids; the choice of single drug versus combinations may vary based on clinical situation and institutional practice. Usually the IT treatment is started at the completion of induction and then given at the start and at count recovery on subsequent consolidations. IT chemotherapy can be omitted during cycles of higher dose cytarabine.

### Post-Consolidation or Maintenance for Patients with APL

Following consolidation therapy, patients are assessed for molecular remission using RT-PCR techniques on bone marrow samples. For patients who have achieved PCR negative status, a 1- to 2-year course of ATRA maintenance therapy, which may be combined with

6-mercaptopurine and methotrexate, may be a reasonable approach. The recommendations for maintenance ATRA arose from several early trials that showed superior RFS for patients receiving ATRA alone or in combination as maintenance therapy. The French APL 93 trial randomized eligible patients (n = 289) to four different maintenance regimens: no maintenance, continuous chemotherapy with 6-mercaptopurine and methotrexate, intermittent ATRA, and the combination of ATRA with 6-mercaptopurine and methotrexate.[138] Results showed decreased 2-year relapse rates with continuous chemotherapy (11.5% vs. 27% with no chemotherapy) and with ATRA (13.5% vs. 25% with no ATRA). The estimated 2-year relapse rate for patients who received maintenance with ATRA in combination with chemotherapy was 7.4%, suggesting an additive benefit with the combination. The 2-year EFS rate was also improved with continuous chemotherapy (92% vs. 77% without chemotherapy) and with ATRA (87% vs. 82% without ATRA); the 2-year EFS rate among patients who received ATRA in combination with chemotherapy was 93%.[138] Results from the long-term follow-up of the APL 93 study showed a beneficial effect of maintenance treatment with intermittent ATRA and continuous chemotherapy, with an additive effect of the 2 modalities. The 10-year cumulative relapse rates with no maintenance, ATRA alone, continuous chemotherapy, and ATRA combined with chemotherapy were 43%, 33%, 23%, and 13%, respectively ($P < .001$).[154] Patients considered to be at high risk (WBC count >5000/mcL) appeared to derive the most benefit from maintenance therapy. The 10-year cumulative relapse rate among patients with high-risk disease with no maintenance, ATRA alone, continuous chemotherapy, and ATRA combined with chemotherapy was 68%, 53%, 33%, and 21%, respectively ($P < .001$). No statistically significant difference in the 10-year relapse rates was observed among patients with lower-risk disease, although the relapse rate dropped from 29% without maintenance to 11.5% with ATRA combined with chemotherapy. Overall, the 10-year OS rates with no maintenance, ATRA alone, continuous chemotherapy, and ATRA combined with chemotherapy were 74%, 88%, 93%, and 94%, respectively ($P < .001$).[154]

The first North American Intergroup trial showed superior DFS outcomes for patients receiving maintenance ATRA compared with no maintenance.[153] In this trial, patients were randomized to induction therapy with daunorubicin plus cytarabine or with ATRA alone, and subsequently underwent a second randomization to maintenance therapy with ATRA or no maintenance (observation only). Consolidation therapy comprised the initial induction therapy regimen for course 1, and then daunorubicin and HiDAC for course 2. The 5-year DFS rates for the four randomization groups, chemotherapy induction plus observation, chemotherapy induction plus ATRA maintenance, ATRA induction plus observation, and ATRA induction plus ATRA maintenance, were 16%, 47%, 55%, and 74%, respectively.[153] Thus, the incorporation of ATRA during induction and maintenance appeared to improve long-term remission durations. It should be noted that in the above North American Intergroup trial, molecular remission status was not assessed prior to randomization to maintenance treatment.

The Japanese APL 97 randomized study evaluated the role of maintenance with intensified chemotherapy compared with observation in patients with APL who achieved molecular remission following consolidation (n = 175).[182] The estimated 6-year DFS was not significantly different between the chemotherapy maintenance and observation arms (63% vs. 80%). In fact, the estimated 6-year OS was significantly lower with maintenance (86% vs. 99%; $P = .014$), which the investigators attributed to possible effects of chemotherapy maintenance on the development of secondary malignancies and responses to subsequent (second-line) therapies.[182]

Data from the AIDA 0493 trial suggested that there was no long-term benefit to maintenance therapy (ie, combination chemotherapy with

6-mercaptopurine and methotrexate, ATRA alone, or ATRA in combination with chemotherapy) in patients who achieved molecular remission (PCR negative) at the end of consolidation therapy.[183] In this trial, ATRA was not given during consolidation. The above studies have not demonstrated long-term benefit with the use of maintenance therapy in patients who achieve molecular remission following consolidation therapy. Further data from randomized trials are needed to address the question of maintenance. A phase III cooperative group trial (SWOG 0521) is designed to examine the need for maintenance therapy (using the combination of ATRA, 6-mercaptopurine, and methotrexate) in patients with low-risk APL. In this trial, patients receive induction therapy with ATRA, daunorubicin, and cytarabine, followed by consolidation therapy with ATO, ATRA, and daunorubicin. Patients are then randomized to receive maintenance therapy or no further treatment (observation only). No benefit for maintenance was observed.[184] The benefit of maintenance therapy likely depends on the regimens used during induction and consolidation therapies. Therefore, it is important to use maintenance therapy in conjunction with the treatment protocols in which they have been shown to confer benefit.

RT-PCR should be performed on a blood sample at completion of consolidation to document molecular remission. It is at the discretion of the treating physician to determine the appropriate frequency of monitoring for individual patients. Periodic monitoring is recommended for up to 2 years during maintenance therapy to detect molecular relapse in patients with high-risk disease, patients >60 years of age or who had long interruptions during consolidation, or patients on regimens that use maintenance and are not able to tolerate maintenance. Clinical experience indicates that the risk of relapse in patients with low-risk disease who have achieved molecular remission at completion of consolidation is low, and monitoring may not be necessary outside the setting of a clinical trial. At the current level of test sensitivity/specificity, a change from PCR negative to positive status should be confirmed in a blood sample by a reliable laboratory within 2 to 4 weeks. If molecular relapse is confirmed by a second positive test, the patient should be treated for relapsed disease (see *APL: Therapy for Relapse* in the algorithm). If the second test was negative, maintenance therapy and frequent monitoring (eg, every 2–3 months) for up to an additional 2 years may be considered to ensure that the PCR remains negative. Testing should be done in the same laboratory to maintain a consistent level of sensitivity. For patients who develop cytopenias and who have a negative RT-PCR, a bone marrow aspirate is recommended to assess for new cytogenetic abnormalities, as secondary MDS and AML can occur following APL therapy.

**Management of Relapsed APL**

ATO is recommended for patients who do not achieve molecular remission at completion of consolidation or who subsequently demonstrate molecular or morphologic relapse. As a single agent, ATO produced CR rates of 80% to 90% in patients with hematologic relapse and achieved molecular remissions in 70% to 80% of those patients.[165,185-187] In a retrospective analysis of patients with APL who experienced relapse after first-line therapy with ATRA combined with chemotherapy (n = 23), reinduction therapy with ATO-containing regimens (ATO monotherapy, n = 20; ATO combined with ATRA and anthracycline, n = 2; ATO combined with mitoxantrone, n = 1) resulted in hematologic CR in 95% and molecular remission in 83% of patients.[188] ATRA and ATO appear to be synergistic and one could consider using the combination in patients who have not received ATRA during consolidation.[164-166] However, in a small randomized study of patients with relapsed APL (n = 20), all patients previously treated with ATRA-containing chemotherapy showed no improvement in response by adding ATRA to ATO compared with ATO alone.[189] The role of retreatment with ATO for patients who experience relapse following therapy with ATO-containing regimens during initial induction and/or consolidation therapy remains unknown. A retrospective

analysis in a small number of patients reported a second CR rate of 93% (both for hematologic CR and molecular remission) among patients who were retreated with ATO combined with ATRA (with or without anthracyclines) after a relapse following first-line therapy with single-agent ATO (n = 14).[188]

For patients with APL who experience relapse early (<6 months) after an initial CR to first-line therapy with ATRA and ATO with no prior exposure to anthracyclines, anthracycline-based regimens (ATRA plus daunorubicin and cytarabine[153,155,156]; and AIDA alone[157]) are recommended. For patients who experience an early relapse (<6 months) after an initial CR to ATRA and anthracycline-containing first-line regimens or with no prior exposure to ATO, it is recommended that the patient receive ATO with or without ATRA, and with or without a single dose of GO until count recovery with marrow confirms remission. For patients who experience a late relapse (≥6 months) to ATO-containing regimens, ATO with or without ATRA, and with or without a single dose of GO/an anthracycline is recommended as first-line therapy after relapse. Following completion of the first cycle of consolidation, if the patient does not achieve molecular remission, a matched sibling or alternative donor (haploidentical, unrelated donor, or cord blood) HCT or clinical trial is recommended. Testing is recommended at least 2 to 3 weeks after the completion of arsenic to avoid false positives.

A small phase II trial in patients with relapsed APL evaluated ATO during induction and consolidation followed by a peripheral blood hematopoietic cell harvest after HiDAC chemotherapy and autologous HCT.[190] The study enrolled 35 patients (16 who experienced hematologic relapse and 9 who experienced molecular relapse) between the ages of 18 and 65 years. The EFS after 1 year was 77% (90% CI, 63%–86%). At a median follow-up of 4.9 years (range, 0.3–6.3 years), the 5-year EFS was 65% and the 5-year OS was 77% with an estimated 59% probability of failure-free survival.[190] The data suggest that this sequential treatment regimen may provide improved outcomes with greater duration.

A retrospective analysis conducted by the European APL Group showed that in patients who received HCT following a second hematologic remission (primarily with ATRA-containing regimens), outcomes were more favorable with autologous HCT (n = 50) compared with allogeneic HCT (n = 23). The 7-year RFS (79% vs. 92%) and EFS (61% vs. 52%) rates did not reach statistical significance between patients who received autologous HCT versus allogeneic HCT; however, 7-year OS rates were significantly improved with autologous compared with allogeneic HCT (60% vs. 52%; *P* = .04).[191] Among patients who received a PCR-negative autograft, the 7-year RFS and OS rates were 87% and 75%, respectively. Although the relapse rates were low with allogeneic HCT, the reduced OS with this procedure was accounted for by the higher treatment-related mortality observed in the allogeneic HCT group compared with the autologous HCT group (39% vs. 6%).[191]

A second study also suggested that autologous transplant could have a survival advantage over allogeneic transplant in this population.[192] Chakrabarty et al[192] looked at 294 patients who received either allogeneic transplant (n = 232) or autologous transplant (n = 62) between 1995 and 2006. The 5-year DFS in the autologous transplant recipients was 63% (range, 49%–75%) versus 50% (range, 44%–57%) in patients receiving allogeneic transplant. Although the DFS was not statistically significant (*P* = .1), the difference in OS did reach statistical significance (*P* = .002). In the patients receiving autologous transplant, OS was 75% (range, 63%–85%) versus 50% (range, 48%–61%). The authors attribute this benefit to the increased treatment-related mortality seen with patients receiving allogeneic transplant (30%) compared to autologous transplant (2%).

It should be noted that only limited evidence from retrospective studies exist with regard to the role of autologous and allogeneic HCT following

relapse of APL in the era of ATO therapy. The optimal consolidation strategy following therapy with ATO-containing regimens in patients with relapsed disease remains to be defined.[193] In a small retrospective study of patients with relapsed APL treated with ATO-containing induction and consolidation therapy, outcome of further consolidation with autologous HCT was compared with maintenance (without autologous HCT) consisting of ATO with or without ATRA.[188] In this analysis, all patients had achieved second molecular remission following induction and consolidation therapy with the ATO-containing regimens; subsequently, 14 patients underwent autologous HCT and 19 patients opted for an ATO-containing maintenance regimen. Consolidation with autologous HCT was associated with a significantly higher 5-year EFS rate (83% vs. 34.5%; *P* = .001) and OS rate (100% vs. 38.5%; *P* = .001) compared with ATO-containing maintenance therapy.[188] The authors concluded that consolidation with autologous HCT was superior to ATO-containing maintenance alone in patients who achieved molecular remission after relapse. Outcome data from the ELN registry reported a 3-year OS after transplant in second CR of 80% compared with 59% in patients without transplant (*P* = .03).[194]

In the context of a clinical trial or on compassionate use, GO is a potential treatment option for relapsed APL. The voluntary withdrawal of the drug in 2010 was based on interim data from a randomized trial in adult patients (aged 18–60 years) with AML comparing induction regimens of cytarabine and daunorubicin with or without GO in which there was no improvement in outcomes and a small but significant increase in early mortality in the GO arm.[195] Subsequent results of this trial eventually showed no difference in overall mortality between the two arms.[196] Since its withdrawal from the market, studies have demonstrated a significant benefit for GO in specific patient populations. Therefore, GO has been re-approved for AML. One complication to evaluating the benefit of GO is that APL occurs in a small population of patients, and therefore studies do not have the numbers to enroll for a suitable trial. The benefit of GO must be weighed against the possibility for adverse events. Clinicians should be advised of the possible complication of sinusoidal obstructive syndrome when administering GO.

A small percentage of relapsed APL has a CNS component.[197,198] Therefore, for patients who are in second morphologic remission, the use of IT therapy for CNS prophylaxis should be considered. Patients who achieve a molecular remission after second-line therapy should be considered for autologous HCT if they do not have contraindications to high-dose therapy. Allogeneic transplant should be reserved for patients who have persistent disease despite therapy for relapsed disease. For patients in second CR who have contraindications to HCT, continued therapy with ATO for six cycles is recommended in the absence of a suitable clinical trial.

### Supportive Care for Patients with APL

Specific supportive care issues should be considered when treating patients with APL. Therapy for APL is often associated with a constellation of symptoms and physiologic abnormalities, including fluid retention, dyspnea, episodic hypotension, pulmonary infiltrates, and pulmonary or pericardial effusions now referred to as “differentiation syndrome.” Approximately 15% to 25% of previously untreated patients receiving ATRA-containing therapy develop this syndrome.[199,200] Patients may begin to develop evidence of differentiation syndrome early in the treatment with either ATRA or ATO as single agents or in combination. These patients develop fever, often accompanied by rapidly rising WBC counts (>10,000/mcL). Patients should be closely monitored for hypoxia and the development of pulmonary infiltrates or pleural effusion. Differentiation syndrome along with hemorrhage are the leading causes of death during induction therapy. Early recognition and prompt initiation of corticosteroids are key components in the management of this complication. In some

studies, low mortality and morbidity rates were reported when corticosteroids were administered prophylactically in patients presenting with high WBC counts.[161,201] Kelaidi et al[202] assessed the outcomes of patients with high WBC (>10,000/mcL) enrolled in the APL 93 and APL 2000 trials.[202] A fundamental difference between these two trials was the use of dexamethasone (10 mg every 12 hours beginning on day 1) for patients on APL 2000. The early death rate from differentiation syndrome dropped from 8 in 139 patients (6%) in the APL 93 trial to 2 in 133 patients (1.5%) in the APL 2000 trial.

There should be a high index of suspicion for differentiation syndrome in APL patients who may be triggered by symptoms including fever, an increasing WBC count greater than 10,000/mcL, shortness of breath, hypoxemia, and pleural or pericardial effusion. Close monitoring of volume overload and pulmonary status is warranted in these patients and initiation of dexamethasone should occur at the first signs or symptoms of respiratory compromise (ie, hypoxia, pulmonary infiltrates, pericardial or pleural effusions). The NCCN AML Panel recommends treating with dexamethasone 10 mg twice daily for 3 to 5 days, then tapering the dose over 2 weeks (see *Principles of Supportive Care for APL* in the algorithm). ATRA may need to be withheld during the initial acute symptomatic period but may be resumed when symptoms resolve. Other factors that have been reported to increase the risk of differentiation syndrome include a high body mass index and age >40 years. For patients at high risk (WBC count >10,000/mcL) of developing differentiation syndrome, initiate prophylaxis with corticosteroids, either prednisone (0.5 mg/kg) from day 1 or dexamethasone 10 mg every 12 hours (see *Principles of Supportive Care for APL* in the algorithm). The steroid dose should be tapered over a period of several days. It is recommended that the prophylaxis regimen follow the specific treatment protocol used. In the Australia/New Zealand study that evaluated induction with ATO added to a backbone of AIDA (phase II APML4 trial), all patients received prednisone (1 mg/kg/day for at least 10 days) as prophylaxis for differentiation syndrome regardless of initial WBC count [see *APL Treatment Induction (High Risk)* in the algorithm].[173] In the Italian-German Cooperative Group study that evaluated ATRA combined with ATO versus the AIDA regimen (phase III APL0406 trial), patients received prophylaxis with prednisone (0.5 mg/kg/day) from day 1 until the end of induction [see *APL Treatment Induction (Low Risk)* in the algorithm].[159] If a patient develops differentiation syndrome, it is recommended that treatment be changed from prednisone to dexamethasone 10 mg every 12 hours until count recovery or risk of differentiation has abated.[157,159] In settings where differentiation syndrome is difficult to treat, the panel recommends the following cytoreduction strategies for leukocytosis: hydroxyurea, anthracyclines, and GO.

Leukapheresis is not routinely recommended in the management of patients with high WBC counts in APL because of the difference in leukemia biology. However, in cases of potentially life-threatening leukostasis not responsive to other modalities, leukapheresis can be considered with caution.

Because coagulopathy is common in patients with APL, it is important to screen for this problem with evaluation of prothrombin time, partial thromboplastin time, and fibrinogen concentration during the initial workup and before any invasive procedure. Clinical coagulopathy is managed by aggressive transfusion support to maintain platelet counts of 50,000/mcL or greater, by fibrinogen replacement with cryoprecipitate and frozen plasma to maintain a level of 150 mg/dL, and by maintenance of prothrombin time and partial thromboplastin time close to normal. Patients with clinical coagulopathy need to be monitored daily until resolution. Given the risks of coagulopathy in APL at diagnosis, invasive procedures including leukapheresis and/or central line placement should be avoided. If possible, the diagnosis of APL may be made using peripheral blood

samples, which may minimize the risk of bleeding complications until coagulopathy can be adequately controlled.

ATO therapy may prolong the QT interval, making patients susceptible to ventricular arrhythmias. Therefore, prior to initiation of therapy, an ECG is recommended to assess the QT interval. Routine monitoring (eg, weekly) during therapy is suggested for patients who are older. Serum electrolytes should also be monitored prior to and during therapy to maintain electrolytes within the middle or upper normal range. Other drugs that prolong the QT interval should be avoided during ATO therapy to minimize the risk of cardiac arrhythmias. Patients with an absolute QTc interval greater than 500 milliseconds should be reassessed on a weekly basis during induction therapy, and prior to each course of post-remission therapy. A cardiology consult may be appropriate for patients with prolonged QTc and when QTcF corrections are unavailable.[203]

Growth factors are not recommended during induction for patients with APL as they can complicate assessment of response and increase the risk of differentiation syndrome. There is no evidence for whether growth factors have a positive or negative impact on long-term outcome if used during consolidation. However, growth factors may be considered during consolidation in selected cases, including in the event of life-threatening infections, or when signs/symptoms of sepsis are present, in an attempt to shorten the duration of neutropenia.

## Management of Acute Myeloid Leukemia

Most initial treatment decisions for AML are based on age, history of prior myelodysplasia or cytotoxic therapy, and performance status. Although karyotype and molecular markers are powerful predictors of DFS outcomes, induction chemotherapy will be initiated before this information is available in most instances. The intent of traditional induction chemotherapy is to produce a major reduction in the leukemic burden and to restore normal hematopoiesis. Early in the process of developing a treatment plan, it is reasonable to consider referral to palliative care for consultation.[204,205]

Recommendations for induction chemotherapy in patients with AML consider age 60 years as a therapeutic divergence point. This is based on the higher prevalence of unfavorable cytogenetics and antecedent myelodysplasia, along with a higher incidence of multidrug resistance in patients >60 years, and an increased frequency of comorbid medical conditions that affect the patient's ability to tolerate intensive treatment.[206] Because complete remission rates rarely exceed 70% in younger patients and 50% in patients who are older, substantial opportunity exists for innovative clinical trials involving both patient populations. The guidelines consider recommendations for patients younger than or >60 years of age separately.

### Management of AML in Patients Younger Than 60 Years

#### *Induction Therapy*

Standard induction regimens used for patients younger than age 60 years are based on a backbone of cytarabine plus an anthracycline. Historically, in most large cooperative group trials, daunorubicin has been the most commonly used anthracycline at doses of 45 to 60 mg/m$^2$ daily for 3 days. Idarubicin, which has a longer intracellular retention time, used at doses of 12 mg/m$^2$ daily for 3 days, has had comparable remission rates with fewer patients requiring additional therapy at day 15 to achieve remission. CR rates for patients who are 50 years or younger have consistently been in the range of 60% to 70% in most large cooperative group trials of infusional cytarabine and anthracycline. Recent studies have incorporated targeted strategies according to cytogenetics and molecular abnormalities, and the current NCCN Guidelines for AML outline treatment strategies according to these cytogenetic risk groups.

***Risk-Stratified Treatment Strategies***

***Favorable-Risk Cytogenetics***

***Cytarabine and anthracycline dose during induction:*** A large randomized phase III study (E1900) from the ECOG reported a significant increase in CR rate (71% vs. 57%; *P* < .001) and median OS (24 vs. 16 months; *P* = .003) using daunorubicin 90 mg/m$^2$ daily for 3 days (n = 327) versus 45 mg/m$^2$ daily for 3 days (n = 330) in patients with previously untreated AML younger than 60 years.[207] Based on subgroup analyses, however, the survival benefit with high-dose daunorubicin was shown to be restricted to patients with favorable- and intermediate-risk cytogenetic profiles (median OS, 34 vs. 21 months; *P* = .004) and those younger than 50 years (median OS, 34 vs. 19 months; *P* = .004). The survival outcome for patients with unfavorable cytogenetics was poor, with a median OS of only 10 months in both treatment arms.[207] In an update of the E1900 trial, high-dose daunorubicin maintained a higher response than standard-dose daunorubicin in patients younger than 50 years of age (HR, 0.66; *P* = .002).[208] This benefit was seen regardless of cytogenetic risk profile. In addition, patients with *FLT3*-ITD, *DNMT3A*, and *NPM1* mutant AML had improved OS. Patients between 50 and 60 years of age with *FLT3*-ITD or *NPM1*mutant AML also benefitted from high-dose daunorubicin.[208] High-dose daunorubicin was previously evaluated in a European trial that compared idarubicin 12 mg/m$^2$ daily for 3 or 4 days versus daunorubicin 80 mg/m$^2$ daily for 3 days in patients between ages 50 and 70 years; CR rates were 83%, 78%, and 70%, respectively (*P* = .04).[209] No difference was seen in relapse rate, EFS, or OS outcomes between the treatment arms.

In a systematic review and meta-analysis of 29 randomized controlled trials (RCTs) comparing idarubicin to daunorubicin,[210] idarubicin had a lower remission failure rate compared to daunorubicin (RR, 0.81; 95% CI, 0.66–0.99; *P* = .04), but no difference was observed in early death or overall mortality. Furthermore, this benefit was only seen when the dose ratio between daunorubicin and idarubicin was less than 5. Both high-dose daunorubicin and idarubicin resulted in 5-year survival rates between 40% and 50%.[210]

It has been suggested that a dose of 60 mg/m$^2$ daunorubicin may be equally as effective as 90 mg/m$^2$ and have a lower toxicity. A study from Burnett et al[211] compared these two doses in 1206 patients who were predominately younger than 60 years of age. There was no difference in CR (73% vs. 75%; OR, 1.07; 95% CI, 0.83–1.39; *P* = .60). The 60-day mortality was higher in the patients receiving 90 mg/m$^2$ (10% vs. 5%; HR, 1.98; 95% CI, 1.30–3.02; *P* = .001), though the 2-year OS was similar (59% vs. 60%; HR, 1.16; 95% CI, 0.95–1.43; *P* = .15).[210] It is worth noting that all patients received a second course of chemotherapy that included additional daunorubicin (50 mg/m$^2$) on days 1, 3, and 5, which may potentially have mitigated the effects of a 90 mg/m$^2$ daunorubicin dose.

***CD33-Positive AML:*** GO is a humanized anti-CD33 monoclonal antibody conjugated with the cytotoxic agent calicheamicin,[212] that was initially approved in the year 2000 as a monotherapy for AML based on data from single-arm phase II trials for older adult patients in first relapse.[213] The voluntary withdrawal of the drug in 2010 was based on interim data from a randomized trial in adult patients (aged 18–60 years) with AML comparing induction regimens of cytarabine and daunorubicin with or without GO in which there was no improvement in outcomes and a small but significant increase in early mortality in the GO arm.[195] Subsequent results of this trial eventually showed no difference in overall mortality between the two arms.[196] Since its withdrawal from the market, studies have demonstrated a significant benefit for GO in specific patient populations. In the MRC AML 15 trial, the efficacy and safety of adding GO (3 mg/m$^2$ on day 1 of induction) to three induction regimens, including daunorubicin (50 mg/m$^2$ on days 1, 3, and 5) and cytarabine (100 mg/m$^2$ on days 1–10 every 12 hours), was evaluated in patients 60 years or younger with previously

untreated AML (n = 1,113).[214] The addition of GO was well tolerated and there were no differences in RFS or OS rates between arms that received or did not receive GO. The patients predicted to derive significant benefit with the GO addition to chemotherapy included those with favorable-risk cytogenetics, with a trend towards benefit for those with intermediate-risk cytogenetics.[214] A meta-analysis of five randomized trials (including adult patients ≥60 years) showed that adding GO (including alternative dosing schedules) to conventional induction therapy also provides survival benefit.[215] A review of these and other studies (see *Management of AML in Patients Older than 60 Years*) led to the approval of GO in September 2017 for the treatment of adults with newly diagnosed CD33-positive AML.

In the MRC AML 15 trial, younger patients with untreated AML (median age, 49 years), were randomized to two induction courses of: 1) daunorubicin and cytarabine (DA) with or without etoposide (ADE; n = 1983); or 2) ADE versus fludarabine, cytarabine, granulocyte colony-stimulating factor (G-CSF), and idarubicin (FLAG-Ida; n = 1268).[216] Patients in the DA and FLAG-Ida arms were randomly assigned to a single dose of GO (3 mg/m$^2$) during the first induction course.[216] Patients with favorable- and intermediate-risk disease who received two induction courses of FLAG-Ida with GO in course 1, followed by 2 courses of HiDAC had an 8-year survival rate from remission of 72% (favorable risk, 95%; intermediate risk, 63%).[216]

***KIT-Mutated AML:*** Emerging studies are evaluating the impact of adding dasatinib, a TKI, to AML therapy in CBF-AML with *KIT* mutations.[217,218]

***Intermediate-Risk Cytogenetics***

***FLT3-Positive AML:*** The majority of *FLT3*-mutated AML cases occur in patients with intermediate-risk cytogenetics. Data have demonstrated improved survival for patients with newly diagnosed *FLT3*-mutation–positive AML when midostaurin is added to standard chemotherapy as part of frontline treatment.[219-221] This led to its breakthrough designation and approval by the FDA in 2017. In the CALGB 10603/RATIFY Alliance trial, patients aged 18 to 59 years, with newly diagnosed *FLT3*-mutation–positive AML (ITD or TKD) were randomized (n = 717) to receive standard cytarabine therapy (200 mg/m$^2$ daily for 7 days via continuous infusion) and daunorubicin (60 mg/m$^2$ on days 1–3) with placebo or midostaurin (50 mg, twice daily on days 8–21).[221] If residual disease in the bone marrow was observed on day 21, patients were treated with a second blinded course. Patients who achieved CR received 4 28-day cycles of HiDAC (3 g/m$^2$ every 12 hours on days 1, 3, and 5) with placebo or midostaurin (50 mg, twice a day on days 8–21) followed by a year of maintenance therapy with placebo or midostaurin (50 mg twice a day).[221] The median OS was 74.7 months (95% CI, 31.5–not reached [NR]) in the midostaurin group compared to 25.6 months (95% CI, 18.6–42.9) in the placebo group (*P* = .009).[221] Patients who received midostaurin with standard induction and consolidation therapy experienced significant improvement in OS (HR for death, 0.78; *P* = .009) and EFS (HR for event or death, 0.78; *P* = .002) compared with those on the placebo arm.[221]

Some studies suggest that a higher dose of daunorubicin (90 mg/m$^2$), compared to lower doses of either 45 or 60 mg/m$^2$, is significantly associated with increased CR and survival rates in patients with intermediate-risk cytogenetics and those who have *FLT3*-ITD mutation–positive AML.[222,223] A phase III study compared idarubicin (12 mg/m$^2$ for 3 days) and high-dose daunorubicin (90 mg/m$^2$ for 3 days) with standard cytarabine therapy during induction in young adults with newly diagnosed AML (age range, 15–65 years). It was determined that high-dose daunorubicin was associated with higher OS and EFS rates in patients with *FLT3*-ITD mutation–positive AML.[224] However, these studies did not include midostaurin.

***Therapy-Related AML or Antecedent MDS/CMML or AML-MRC***

Although most cases of AML are *de novo*, secondary AML and therapy-related AML account for approximately 25% of all AML cases and are associated with poor outcomes.[225,226] Emerging data have demonstrated improved survival in patients who are older with secondary AML when a dual-drug liposomal formulation of cytarabine and daunorubicin in a 5:1 molar ratio (CPX-351) is used as frontline therapy.[227-229] In a phase II trial, newly diagnosed patients ≥60 years of age with AML (n = 126), were randomized 2:1 to first-line CPX-351 or the conventional administration of cytarabine and daunorubicin (7+3 regimen).[228] Compared to the standard 7+3 regimen, CPX-351 produced higher response rates (CPX-351, 66.7% vs. 7+3, 51.2%; *P* = .07), however differences in EFS and OS were not statistically significant.[228] A planned analysis of the secondary AML subgroup demonstrated that CPX-351 was associated with a higher CR rate (57.6% vs. 31.6%; *P* = .06).[228] These results led to the development of a randomized phase III study comparing the efficacy and safety of CPX-351 to the conventional administration of cytarabine and daunorubicin (control arm) in patients 60–75 years of age with newly diagnosed secondary AML (n = 309).[229] With a median follow-up of 20.7 months, CPX-351 significantly improved OS compared to the control arm (median, 9.56 vs. 5.95 months; HR, 0.69; 95% CI, 0.52-0.90; *P* = .003).[229] CPX-351 was also associated with significantly higher overall remission (47.7% vs. 33.3%; *P* = .016) and CR (37.3% vs. 25.6%; *P* = .04) rates. The most frequently reported grade 3 to 5 adverse events in the CPX-351 and control groups were febrile neutropenia (68.0% vs. 70.9%), pneumonia (19.6% vs. 14.6%), and hypoxia (13.1% vs. 15.2%).[229]

***Other Regimens for Intermediate- or Poor-risk Cytogenetics***

***HiDAC-Containing Regimens:*** The use of HiDAC as induction therapy continues to be a controversial approach. The most recent study from the EORTC-GIMEMA AML-12 trial suggests that HiDAC (3 g/m$^2$ every 12 hours on days 1, 2, 5, and 7) improves outcome in patients who are younger than 46 years of age.[230] This study randomized 1900 patients between the ages of 15 and 60 years into two treatment groups, HiDAC and standard-dose cytarabine (SDAC; 100 mg/m$^2$/d by continuous infusion for 10 days). Both groups were also given daunorubicin (50 mg/m$^2$/d on days 1, 3, and 5) and etoposide (50 mg/m$^2$/d on days 1–5). Data from a median 6-year follow-up indicate an OS near statistical significance (HiDAC, 42.5% vs. SDAC, 38.7%; *P* = .06), and when separated by age with a cutoff of 46 years, the benefit was relegated to the younger patient cohort (HiDAC, 51.9% vs. SDAC, 43.3%; *P* = .009) compared to patients ≥46 years of age (HiDAC, 32.9% vs. SDAC, 33.9%; *P* = .91). Other populations that benefited from HiDAC were patients with high-risk disease, including patients with very poor-risk cytogenetic abnormalities and/or *FLT3*-ITD mutation-positive AML or with secondary AML. There was no significant increase in grade 3 or 4 toxicities except for an increase in conjunctivitis (grade 2–3) with HiDAC (12.4%) versus SDAC (0.5%). Incidence of adverse events was equivalent (SDAC, 67.6% vs. HiDAC, 66.2%). Patients in CR received a single consolidation cycle of daunorubicin and cytarabine (500 mg/m$^2$ every 12 hours for 6 days) and subsequent HCT.[230]

HiDAC therapy during induction was initially explored two decades ago in 2 large cooperative group trials. In an Australian Leukemia Study Group trial,[231,232] patients younger than 60 years were randomized (n = 301) to receive either HiDAC (3 g/m$^2$ every 12 hours on days 1, 3, 5, and 7 for a total of 24 g/m$^2$) or standard cytarabine therapy (100 mg/m$^2$ daily for 7 days via continuous infusion); patients in both arms received daunorubicin (50 mg/m$^2$ on days 1–3) and etoposide (75 mg/m$^2$ daily for 7 days). The CR rates were equivalent in both arms (71% and 74%, respectively), and a significantly higher 5-year RFS rate was observed in the HiDAC arm (48% vs. 25%; *P* = .007).[232] Patients in both treatment arms received only 2 cycles of standard-dose cytarabine, daunorubicin, and etoposide for consolidation therapy. Median remission duration was 45 months for the

high-dose arm, compared with 12 months for the standard treatment arm.[231] However, treatment-related morbidity and mortality were higher in the HiDAC arm; the 5-year OS rates were 33% in the high-dose arm compared with 25% in the standard-dose arm.[232]

In a large SWOG study,[233] patients younger than 65 years (n = 665) with *de novo* or secondary AML were randomized to receive HiDAC (2 g/m$^2$ every 12 hours for 6 days for a total of 24 g/m$^2$; patients aged <50 years were initially randomized to receive 3 g/m$^2$ at the above schedule before the high-dose arm was redefined to 2 g/m$^2$ because of toxicity concerns) or standard-dose cytarabine (200 mg/m$^2$ daily for 7 days); patients in both treatment arms also received daunorubicin (45 mg/m$^2$ daily for 3 days). Patients treated in the HiDAC arm received a second high-dose cycle for consolidation, whereas patients in the standard-dose arm were randomized to receive consolidation therapy with either 2 cycles of standard-dose cytarabine or 1 cycle of HiDAC plus daunorubicin. The CR rates were similar, with 55% for the high-dose arm compared with 58% for the standard-dose arm for patients younger than 50 years, and 45% for HiDAC versus 53% for standard-dose therapy for patients 50 to 65 years of age. DFS rate (for patients who achieved a CR) and OS rate (for all patients) at 4 years were not significantly different among treatment arms. Induction therapy with HiDAC was associated with significantly higher rates of treatment-related mortality (14% vs. 5% for patients aged <50 years; 20% vs. 12% for patients aged 50–64 years; $P$ = .003) and grade 3 or higher neurologic toxicity (8% vs. 2% for patients aged <50 years; 5% vs. 0.5% for patients aged 50–64 years; $P$ < .0001).[233] For patients younger than 50 years, consolidation with HiDAC was associated with similar rates of treatment-related mortality (2% vs. 0%) and grade 3 or higher neurologic toxicity (2% vs. 0%) compared with the standard dose. For the original cohort of patients younger than 50 years who received 3 g/m$^2$ HiDAC for induction, the rates of treatment-related deaths (10% vs. 5%) and grade 3 or greater neurologic toxicity (16% vs. 2%) were higher than for those who received the standard dose. Similarly, for patients younger than 50 years who received 3 g/m$^2$ HiDAC for consolidation, the rates of treatment-related deaths (4% vs. 0%) and grade 3 or greater neurologic toxicity (16% vs. 0%) were higher than for those who received the standard dose.[233]

Younger patients (age <50 years) who received HiDAC induction and consolidation in the SWOG trial had the highest OS and DFS rates at 4 years (52% and 34%, respectively) compared with those who received standard-dose induction and consolidation (34% and 24%, respectively) or standard induction with high-dose consolidation (23% and 14%, respectively).[233] However, the percentage of patients achieving a CR who did not proceed to consolidation was twice as high in the HiDAC induction arm.[233] The risks for neurotoxicity and renal insufficiency are increased with HiDAC; therefore, both renal and neurologic function should be closely monitored in patients receiving this treatment. In a CALGB trial,[234] the subgroup of patients aged 60 years or younger (n = 156) who received standard-dose cytarabine-daunorubicin induction therapy and 4 courses of HiDAC consolidation (3 g/m$^2$ every 12 hours on days 1, 3, and 5, per course) experienced a 4-year DFS rate of 44%. Among all patients who received consolidation with HiDAC, the rates of treatment-related deaths and serious neurotoxicity were 5% and 12%, respectively.[234]

Because the OS outcomes for the high-dose arm in the SWOG trial consisting of HiDAC induction and 2 cycles of HiDAC consolidation (4-year OS rate of 52% for patients aged <50 years) were comparable to those of the CALGB trial with standard-dose infusional cytarabine induction and 4 cycles of HiDAC consolidation (4-year OS rate of 52% for patients aged ≤60 years), the use of HiDAC in the induction phase outside of a clinical trial remains controversial. A meta-analysis including 22 trials and 5945 patients with de novo AML younger than 60 years of age demonstrated improved RFS and reduced risk of relapse, particularly in the setting of

favorable-risk cytogenetics, for patients receiving HiDAC versus standard chemotherapy.[235] However, toxicity was a limiting factor and emphasis was placed on the importance of future studies to define the populations that would most benefit from HiDAC and to optimize dosing recommendations. The decision to use high- versus standard-dose cytarabine for induction might be influenced by consolidation strategies; fewer high-dose consolidation cycles may be needed for patients induced with HiDAC or for those who will undergo early autologous HCT. Although the remission rates are similar for high- and standard-dose cytarabine, 2 studies have shown more rapid marrow blast clearance after 1 cycle of high-dose therapy and a DFS advantage for patients aged 50 years or younger who received the high-dose therapy.[236] No data are available using more than 60 mg/m$^2$ of daunorubicin or 12 mg/m$^2$ of idarubicin with HiDAC. With either high- or standard-dose cytarabine-based induction for younger patients, between 20% and 45% of these patients will not enter remission. In a report of 122 patients treated with HiDAC and daunorubicin, the remission rates were strongly influenced by cytogenetics, with CR rates of 87%, 79%, and 62% for favorable-, intermediate-, and poor-risk groups, respectively.[237]

As previously mentioned, in the MRC AML 15 trial, younger patients with untreated AML (median age, 49 years), were randomized to two induction courses of: 1) daunorubicin and cytarabine with or without etoposide (ADE; n = 1983); or 2) ADE versus fludarabine, cytarabine, G-CSF, and idarubicin (FLAG-Ida; n = 1268).[216] In consolidation, patients were randomized to amsacrine, cytarabine, etoposide, and then mitoxantrone/cytarabine, or HiDAC (3 g/m$^2$; n = 1445).[216] Patients in the HiDAC arm received 1.5 g/m$^2$ in consolidation, and were treated with or without a fifth course of cytarabine (n = 227). There were no significant differences in the rate of CR between ADE and FLAG-Ida (81% vs. 84%, respectively), but FLAG-Ida significantly decreased relapse rates (FLAG-Ida, 38% vs. ADE, 55%; $P < .001$).[216] A recent randomized phase III study from the HOVON/SAKK groups compared standard cytarabine/idarubicin induction with or without clofarabine (10 mg/m$^2$ on days 1–5) for patients with AML between the ages of 18 to 65 years.[238] While there was no difference in the OS and EFS in the group as a whole, there was a decrease in relapse rate counter balanced by an increased rate of death in remission for the clofarabine arm. In a subset analysis, there was a significant improvement in OS and EFS for the ELN intermediate I group, primarily in patients in the *NPM1* wild-type/*FLT3*-ITD–negative subgroup with a 4-year EFS of 40% for the clofarabine arm versus 18% for the control arm.[238]

***NCCN Recommendations***

The NCCN AML Panel strongly encourages enrollment in a clinical trial for treatment induction of younger patients (aged <60 years) with AML. For patients not enrolled in a clinical trial, cytogenetics and the risk status of the disease guide treatment strategies. For patients with favorable-, intermediate-, and poor-risk cytogenetics, infusional standard-dose cytarabine (100–200 mg/m$^2$ continuous infusion) for 7 days combined with either idarubicin (12 mg/m$^2$ for 3 days) or daunorubicin (60–90 mg/m$^2$ for 3 days) is a category 1 recommendation.[207]

For patients with favorable-risk cytogenetics, other treatment options include standard-dose cytarabine (200 mg/m$^2$ continuous infusion) for 7 days combined with daunorubicin (60 mg/m$^2$ for 3 days) and GO for patients with CD33-positive AML (category 2A and preferred recommendation);[214] or, fludarabine (30 mg/m$^2$ IV for days 2–6) plus HiDAC (2 g/m$^2$) over 4 hours starting 4 hours after fludarabine in combination with idarubicin (8 mg/m$^2$ IV days 4–6) and G-CSF (SC daily on days 1–7) plus a single dose of GO (category 2B recommendation).[216]

For patients with intermediate-risk cytogenetics and *FLT3*-mutated AML, midostaurin is added to standard-dose cytarabine (200 mg/m$^2$ continuous

infusion) for 7 days combined with daunorubicin (60 mg/m$^2$ for 3 days) (category 2A recommendation).[221]

Patients with antecedent hematologic disease or treatment-related AML are considered to have poor-risk disease, unless they have favorable cytogenetics such as t(8;21), inv(16), or t(16;16). In addition, patients with unfavorable karyotypes, such as 11q23 abnormalities, monosomy -5 or -7, monosomal karyotype, or complex cytogenetic abnormalities and mutations including *RUNX1*, *ASXL1*, and *TP53*, are also considered to have poor-risk disease. Although all patients with AML are best treated within the context of an appropriate clinical trial, it is particularly important that this group of patients with poor-risk disease should be entered into a clinical trial (incorporating either chemotherapy or novel agents), if available, given that only 40% to 50% of these patients experience a CR (approximately 25% in adult patients who are older with poor-risk cytogenetics) with standard induction therapy. In addition, HLA testing should be performed promptly in those who may be candidates for either fully ablative or reduced-intensity conditioning (RIC) allogeneic HCT from a matched sibling or an alternative donor, which constitutes the best option for long-term disease control.[239] For younger patients (aged <60 years) with therapy-related AML other than CBF/APL, antecedent MDS/chronic myelomonocytic leukemia (CMML), and cytogenetic changes consistent with MDS (AML-MRC), CPX-351 [cytarabine (100 mg/m$^2$) and daunorubicin (44 mg/m$^2$)] as an intravenous infusion over 90 minutes on days 1, 3, and 5 of 1 cycle is a category 2B recommendation, because the trial did not include this patient population.[229]

Other recommended induction regimens for intermediate- or poor-risk disease include: standard-dose cytarabine (200 mg/m$^2$ continuous infusion) for 7 days combined with daunorubicin (60 mg/m$^2$ for 3 days) and GO for patients with CD33-positive AML (intermediate-risk AML);[214] fludarabine (30 mg/m$^2$ IV for days 2–6) plus HiDAC (2 g/m$^2$) over 4 hours starting 4 hours after fludarabine in combination with idarubicin (8 mg/m$^2$ IV days 4–6) and G-CSF (SC daily on days 1–7) (category 2B recommendation);[216] or HiDAC plus an anthracycline and etoposide (category 1 recommendation for patients 45 years of age or younger, but a category 2B recommendation for other age groups).[230,231,233,236] The study from Willemze et al[230] that demonstrated improved OS for patients between the ages of 15 and 45 years treated on this regimen was integral in the change of the recommendation to category 1 for this age group. For patients with impaired cardiac function, other cytarabine-based regimens combined with non-cardiotoxic agents can be considered. For patients with unfavorable-risk cytogenetics and *TP53*-mutated AML, treatment options are lacking, and alternative strategies should be considered.

***Postinduction Therapy***

***After Standard-Dose Cytarabine Induction***

To judge the efficacy of the induction therapy, a bone marrow aspirate and biopsy should be performed 14 to 21 days after start of therapy. In patients who have received standard-dose cytarabine induction and have significant residual disease without hypoplasia (defined as cellularity less than 20% of which the residual blasts are less than 5% [ie, blast percentage of residual cellularity]), additional therapy with standard-dose cytarabine and anthracycline or escalation to HiDAC (1.5–3 g/m$^2$ every 12 hours for 6 days) may be considered for re-induction; no data are available to determine superiority of standard-dose cytarabine or HiDAC. After a bone marrow biopsy on day 21, standard-dose cytarabine with anthracycline and midostaurin should be considered for patients with *FLT3*-mutated AML.[221] If dual-drug liposomal encapsulation of cytarabine and daunorubicin was given during induction, after a bone marrow biopsy 14–21 days after induction, re-induction with CPX-351 [cytarabine (100 mg/m$^2$) and daunorubicin (44 mg/m$^2$)] as an intravenous infusion over 90 minutes on days 1 and 3 is recommended for patients with therapy-related

AML other than CBF/APL, antecedent MDS/CMML, or AML-MRC.[229] Treatments for induction failure may also be considered.

For patients with significant (>50%) cytoreduction and a low percentage of residual blasts (as defined above), standard-dose cytarabine with idarubicin or daunorubicin, or standard-dose cytarabine with daunorubicin and midostaurin is recommended for patients with for *FLT3*-mutated AML. If daunorubicin (90 mg/m$^2$) was used in induction, the recommended dose for reinduction of daunorubicin prior to count recovery is 45 mg/m$^2$ for no more than 2 doses. Similarly, if idarubicin (12 mg/m$^2$) was used for induction, the early reinduction dose should be limited to 10 mg/m$^2$ for 1 or 2 doses. If the marrow is hypoplastic, additional treatment selection is deferred until the remission status can be assessed.

If hypoplasia status is unclear, a repeat bone marrow biopsy should be considered 5 to 7 days before proceeding with post induction therapy. For patients who achieve CR with the additional post induction therapy, consolidation therapy can be initiated upon count recovery. Screening LP should be considered at first remission before first consolidation for patients with monocytic differentiation, MPAL, WBC count >40,000/mcL at diagnosis, or extramedullary disease.

Patients who have persistent disease following two courses of therapy (including a reinduction attempt based on midcycle marrow) are considered to have experienced primary induction failure. Treatment options include clinical trial or use of chemotherapy regimens used for relapsed/refractory (R/R) disease (see *Management of Relapsed/Refractory AML*). However, the likelihood of achieving a CR with a third chemotherapy regimen is low, at approximately 20%. If the patient did not receive HiDAC for persistent disease at day 15, HiDAC with or without anthracycline may be used if a clinical trial is not available and a donor is not yet identified. If regimens used will result in high cumulative doses of cardiotoxic agents, consider reassessing the patient's cardiac function before each anthracycline/mitoxantrone-containing course.[240] If the patient has an identified sibling or alternative donor available, a transplant option should be explored, although the panel encourages using alternative therapies to achieve remission prior to the transplant. For patients whose clinical condition has deteriorated such that active treatment is not an option, best supportive care should be continued.

***After High-Dose Cytarabine Induction***

Patients initially treated with HiDAC and who have significant residual disease without a hypocellular marrow 21 to 28 days after start of therapy are considered to have experienced induction failure. In the ELN Guidelines, primary induction failure is defined as failure to achieve CR after two courses of intensive induction chemotherapy.[21] Additional HiDAC therapy at this time is unlikely to induce remission in these cases. These patients should be considered for a clinical trial or for use of regimens used for R/R disease (see *Management of Relapsed/Refractory AML*). If an HLA-matched sibling or alternative donor has been identified, an allogeneic HCT may be effective in 25% to 30% of patients who have experienced induction failure. If no donor is immediately available, patients should be considered for a clinical trial. If the patient's clinical condition has deteriorated to a point at which active therapy would be detrimental, best supportive care may be the most appropriate option. If the patient has a significant cytoreduction following HiDAC with a small quantity of residual blasts or hypoplasia, additional therapy should be delayed for an additional 10 to 14 days and the marrow status may be reassessed.

Occasionally, patients with both myeloid and lymphoid markers at diagnosis may experience response to ALL therapy if an AML induction regimen failed.[4] Treatment decisions for patients with significant reduction without hypoplasia or those with hypoplasia are deferred until the blood counts recover and a repeat marrow is performed to document remission status. Response is then categorized as a CR or primary induction failure.

***Post-Remission or Consolidation Therapy***

Although successful induction therapy clears the visible signs of leukemia in the marrow and restores normal hematopoiesis in patients with *de novo* AML, additional post-remission therapy (ie, consolidation) may be needed to reduce the residual abnormal cells to a level that can be contained by immune surveillance. For patients younger than 60 years of age, post-remission therapy is also based on risk status defined by cytogenetics and molecular abnormalities (see *Evaluation for Acute Leukemia* in the algorithm and *Initial Evaluation* in the Discussion).

***High-Dose Cytarabine:*** Since 1994, multiple (3–4) cycles of HiDAC therapy have been the standard consolidation regimen for patients younger than 60 years with either good- or intermediate-risk cytogenetics. This consolidation therapy is based on a CALGB trial comparing 100 mg/m$^2$, 400 mg/m$^2$, and 3 g/m$^2$ doses of cytarabine.[234] The 4-year DFS rate for patients receiving consolidation with 3 g/m$^2$ of HiDAC was 44%, with a 5% treatment-related mortality rate and a 12% incidence of severe neurologic toxicity. Although the initial report did not break down remission duration by cytogenetic groups, subsequent analysis showed a 5-year RFS (continuous CR measured from time of randomization) rate of 50% for CBF AML, 32% for patients with NK-AML, and 15% for patients in other cytogenetic categories (overall $P < .001$). Among the patients who received HiDAC consolidation, the 5-year RFS rate was 78% for CBF AML, 40% for NK-AML, and 21% for other cytogenetic categories.[237]

In some studies, in patients with CBF AML who received postremission therapy with HiDAC, the presence of *KIT* mutations resulted in poorer outcomes, particularly in t(8;21).[37,43] In a multicenter study, patients with CBF AML (n = 67) were enrolled in intensive chemotherapy protocols that involved HiDAC postremission therapy.[37] At 24 months, a *KIT* mutation in the TKD at codon 816 (TKD$^{816}$) in the setting of t(8;21) was associated with a significantly higher incidence of relapse (90% vs. 35.3%, $P = .002$) and lower OS (25% vs. 76.5%, $P = .006$) compared to wild-type KIT.[37] In CBF AML with inv(16), TKD$^{816}$ did not result in a significant difference in relapse incidence and OS.[37] The prognostic influence of TKD$^{816}$ and other mutations in exon 17 (mut*KIT17*) versus other recurrent *KIT* mutations in CBF AML, such as exon 8 (mut*KIT8*), have been investigated.[43,83] In an analysis of adult patients younger than 60 years of age with CBF AML treated on CALGB trials (n = 110), *KIT* mutations (mut*KIT17* and mut*KIT8*) in the setting of inv(16) were associated with a higher cumulative incidence of relapse at 5 years (56% vs. 29%; $P = .05$) and a decreased 5-year OS rate (48% vs. 68%) compared with wild-type *KIT*; in multivariate analysis, the presence of *KIT* mutations remained a significant predictor of decreased OS in the setting of inv(16). In the setting of t(8;21), *KIT* mutations were associated with a higher incidence of relapse at 5 years (70% vs. 36%: $P = .017$), but no difference was observed in 5-year OS (42% vs. 48%).[43] The CALGB trial also included 4 courses of monthly maintenance chemotherapy with daunorubicin and subcutaneous cytarabine after the consolidation phase; however, only 55% of patients who achieved CR received maintenance chemotherapy following HiDAC consolidation.[234] Subsequent clinical trials have eliminated this form of maintenance therapy after post-remission therapy. However, the impact of *KIT* mutations in CBF AML is unclear. A meta-analysis of 11 studies examining the effect of *KIT* mutations on CR, OS, and relapse rates of CBF AML determined that *KIT* mutations did not affect CR rates.[241] In the setting of t(8;21) AML, *KIT* mutations were associated with an increased risk of relapse and shorter OS rates compared to inv(16) AML.[241]

Some studies suggest that after induction, relative to *KIT* mutations, MRD may be a more relevant prognostic factor for CBF-AML risk stratification.[21,242-244] In a prospective study, adult patients with CBF AML (aged 18–60 years; n = 198) were randomized to receive a reinforced induction course (treatment arm A) or standard induction course (treatment arm B), followed by 3 HiDAC consolidation courses.[243]

Treatment arm A consisted of a first sequence with daunorubicin (60 mg/m$^2$/day by a 30 minute IV infusion) on days 1 and 3 and cytarabine (500 mg/m$^2$ continuous infusion) from days 1 to 3, followed by a second sequence at day 8 with daunorubicin (35 mg/m$^2$/day by a 30 minute IV infusion) on days 8 and 9, and cytarabine (1000 mg/m$^2$ every 12 hours by a 2-hour infusion) on days 8 and 10.[243] Treatment arm B consisted of cytarabine (200 mg/m$^2$ continuous infusion) for 7 days combined with daunorubicin (60 mg/m$^2$ for 3 days. In treatment arm B, at day 15 a peripheral blood and BM evaluation was performed followed by a second sequence of chemotherapy in patients who achieved CR.[243] In addition, MRD levels were serially monitored for *RUNX1-RUNX1T1* and *CBFB-MYH11* by real-time quantitative polymerase chain reaction in BM samples before the first, second, and third consolidation courses. In this study, both treatment arms demonstrated similar efficacy. After first consolidation, higher WBC, *KIT* gene mutations and/or *FLT3* gene mutations, and a less than 3-log MRD reduction were associated with a higher specific hazard of relapse, but MRD was the only prognostic factor in multivariate analysis.[243] At 36 months, the cumulative incidence of relapse and RFS were 22% versus 54% ($P$ < .001) and 73% versus 44% ($P$ < .001) in patients who achieved 3-log MRD reduction versus other patients.[243]

A prospective study analyzed the effect of a condensed HiDAC consolidation therapy schedule given on days 1, 2, and 3 versus the commonly used schedule of days 1, 3, and 5 in adult patients (aged 18–60 years) with AML (n = 176), and found that there was no cumulative hematologic toxicity and no change in survival.[245]

The recent shortages of several chemotherapy agents have raised the question of how best to use cytarabine. The HOVON/SAKK study compared a double-induction concept using intermediate-dose cytarabine or HiDAC as part of an induction/consolidation regimen in a phase III randomized study in patients (age 18–60 years) with newly diagnosed AML (n = 860).[23] Patients were randomized to treatment with an "intermediate-dose" cytarabine regimen (12 g/m$^2$ cytarabine; cycle 1: cytarabine, 200 mg/m$^2$ daily for 7 days + idarubicin, 12 mg/m$^2$ daily for 3 days; cycle 2: cytarabine, 1 g/m$^2$ every 12 hours for 6 days + amsacrine, 120 mg/m$^2$ daily for 3 days) or a "high-dose" cytarabine regimen (26 g/m$^2$ cytarabine; cycle 1: cytarabine, 1 g/m$^2$ every 12 hours for 5 days + idarubicin, 12 mg/m$^2$ daily for 3 days; cycle 2: cytarabine, 2 g/m$^2$ every 12 hours for 4 days + amsacrine, 120 mg/m$^2$ daily for 3 days). Patients who achieved a CR after both treatment cycles were eligible to receive consolidation with a third cycle of chemotherapy or autologous or allogeneic HCT.[23] A similar proportion of patients in each treatment arm received consolidation, specifically 26% to 27% of patients who received a third chemotherapy cycle, 10% to 11% of patients who underwent autologous HCT, and 27% to 29% of patients who underwent allogeneic HCT. No significant differences were observed between the intermediate- and high-dose arms in rates of CR (80% vs. 82%), 5-year EFS (34% vs. 35%), or 5-year OS (40% vs. 42%).[23] These results are comparable to those from the CALGB study with HiDAC.[234] More than 50% of patients in each arm had already achieved a CR when they received cycle 2. The 5-year cumulative rate of relapse risk was also similar between treatment arms (39% vs. 27%, respectively).[23] Outcomes were poor for patients with monosomal karyotype at baseline (n = 83), although the high-dose regimen was associated with significantly improved rates of 5-year EFS (13% vs. 0%; $P$ = .02) and OS (16% vs. 0%; $P$ = .02) compared with patients in this subgroup receiving the intermediate-dose. The incidence of grade 3 or 4 toxicities after cycle 1 was higher in the high-dose arm than in the intermediate-dose arm (61% vs. 51%; $P$ = .005), but the incidence of 30-day mortality was the same in both arms (10%).[23] This study suggests that 2 cycles of intermediate-dose cytarabine (1 g/m$^2$ every 12 hours for 6 days; total dose 12 g/m$^2$ per cycle) for each consolidation cycle may be a feasible alternative to 3 cycles of HiDAC (3 g/m$^2$ for 6 doses; total dose of 18 g/m$^2$ per cycle). This study as

well as the MRC AML 15 study[216] suggest that doses of 3 g/m$^2$ of cytarabine are not clearly more effective than lower doses of 1.5–3 g/m$^2$; in the MRC AML 15 trial, the cumulative incidence of relapse was statistically lower for higher dose cytarabine but this did not translate into better RFS.[216]

***Allogeneic Hematopoietic Transplantation:*** In the EORTC/GIMEMA trial, a 43% 4-year DFS rate was reported in the donor group of patients with poor-risk cytogenetics (n = 64; 73% underwent HCT); this was significantly higher than the 4-year DFS rate (18%; *P* = .008) among the no-donor group (n = 94; 46% underwent HCT).[246] The 4-year DFS rate among patients with intermediate-risk AML was 45% for the donor group (n = 61; 75% underwent HCT) and 48.5% for the no-donor group (n = 104; 62.5% underwent HCT).[246] The incidence of relapse was 35% and 47%, respectively, and the incidence of death in CR was 20% and 5%, respectively. The 4-year OS rate among patients with intermediate-risk disease was 53% for the donor group and 54% for the no-donor group.[246]

The SWOG/ECOG trial reported a 5-year survival rate (from time of CR) of 44% with allogeneic HCT (n = 18; 61% underwent HCT) and 13% with autologous HCT (n = 20; 50% underwent HCT) among the subgroup of patients with unfavorable cytogenetics. Moreover, the 5-year survival rate was similar between those allocated to autologous HCT and those intended for chemotherapy consolidation alone (13% and 15%, respectively).[31] The 5-year survival rates (from time of CR) for patients with intermediate-risk cytogenetics were 52% for the allogeneic HCT group (n = 47; 66% underwent HCT) and 36% for the autologous HCT group (n = 37; 59% underwent HCT).[31]

In the UK MRC AML 10 trial, significant benefit with allogeneic HCT was observed for the subgroup of patients with intermediate-risk cytogenetics (but not for those with favorable or high-risk cytogenetics). In this subgroup, the DFS (50% vs. 39%; *P* = .004) and OS rates (55% vs. 44%; *P* = .02) were significantly higher among the donor groups than the no-donor groups.[247]

During the past decade, “normal” cytogenetics have been shown to encompass several molecular abnormalities with divergent risk behaviors.[38] The presence of an isolated *NPM1* or biallelic *CEBPA* mutation improves prognosis to one only slightly less than that of AML with CBF translocations, placing these mutations in the favorable-risk molecular abnormalities category.[38] In contrast, isolated *FLT3*-ITD mutation and NK-AML have an outlook similar to poor-risk cytogenetics.[45] In a report that evaluated the ELN risk classification in a large cohort of patients, for those in the “Intermediate I” risk group (which includes NK-AML with *FLT3* abnormalities and those lacking both *FLT3* and *NPM1* mutations), RFS was more favorable with allogeneic HCT (94 vs. 7.9 months without allogeneic HCT).[107]

***Maintenance Therapy***

***Hypomethylating Agents (HMAs):*** To improve treatment outcomes, some studies have evaluated the efficacy of maintenance therapy with HMAs after induction or allogeneic HCT. CC-486 is a novel oral formulation of azacitidine that allows prolonged exposure in patients with hematologic malignancies.[248,249] In a phase I/II trial evaluating the efficacy of oral azacitidine as maintenance therapy after allogeneic HCT in adult patients (≥18 years) with AML or MDS, patients received 1 of 4 dosing schedules per 28-day cycle for up to 12 cycles.[250] Of 30 patients, 7 received oral azacitidine once daily for 7 days per cycle (n = 3 at 200 mg; n = 4 at 300 mg), and 23 received oral azacitidine for 14 days per cycle (n = 4 at 150 mg; n = 19 at 200 mg [expansion cohort]).[250] At 19 months of follow-up, median OS was not reached and estimated 1-year survival rates were 86% and 81% in the 7-day and 14-day dosing cohorts, respectively.[250]

In the international phase 3 trial, QUAZAR AML-001, investigators evaluated the efficacy of oral azacitidine as post-remission therapy in adult patients (≥55 years of age) who had newly diagnosed AML or secondary AML, and had experienced CR or CRi after induction with intensive therapies but were ineligible for allogeneic HCT (n = 472; median age, 68 years; range, 55–86 years).[251] Within 4 months of attaining CR or CRi, patients were randomized to receive placebo (n = 234) or 300 mg of oral azacitidine (n = 238) once daily on days 1–14 of repeated 28-day treatment cycles.[251] A 21-day dosing schedule was allowed for patients who experienced AML relapse with 5% of 15% blasts in blood or bone marrow while enrolled in the study. This treatment schedule could continue indefinitely or until the presence of >15% blasts, unacceptable toxicity, or allogeneic HCT.[251] At a median follow-up of 41.2 months, median OS was 24.7 months and 14.8 months in the oral azacitidine and placebo arms, respectively (HR, 0.69; 95% CI, 0.55–0.86; *P* = .0009).[251] In addition, the median RFS was significantly prolonged in the oral azacitidine arm at 10.2 months compared to the placebo arm at 4.8 months (HR, 0.65; 95% CI, 0.52–0.81; *P* = .0001).[251] Based on these data, in September 2020, the FDA approved oral azacitidine for continued treatment of patients with AML who achieved first CR or CRi following intensive induction chemotherapy and are not able to complete intensive postremission therapy.

### *NCCN Recommendations*

#### *CBF Cytogenetic Translocations and MRD Negative*

The NCCN AML Panel recommends the following options for consolidation or maintenance therapy in this subgroup: 1) participation in a clinical trial; 2) 3 to 4 cycles of HiDAC (category 1) alone or plus GO for patients with CD33-positive AML; or 3) intermediate-dose cytarabine (1000 mg/m$^2$) plus daunorubicin and GO for patients with CD33-positive AML (category 2A).[214] There are insufficient data to evaluate the use of allogeneic HCT in first remission for patients with AML who are MRD negative and have favorable-risk cytogenetics outside of a clinical trial.[252] Data suggest that the response to treatment is similar regardless of whether the favorable-risk cytogenetics are *de novo* and treatment-related.[252] However, outcomes in the setting of t(8;21) with *KIT* mutations are less favorable. These patients should be considered for either clinical trials targeted toward the molecular abnormality or allogeneic transplantation. In addition, for patients with favorable-risk cytogenetics who are persistently MRD positive after induction and/or consolidation, alternative therapies including allogeneic transplantation, or a clinical trial should be considered.

#### *Intermediate-Risk Cytogenetics and/or Molecular Abnormalities Including MRD Positive*

The panel members agree that transplant-based options (either matched sibling or alternate donor allogeneic HCT) or 3 to 4 cycles of HiDAC affords a lower risk of relapse and a somewhat higher DFS when given as consolidation for patients with intermediate-risk cytogenetics. While 2 to 3 g/m$^2$ HiDAC is preferred, a range of 1 to less than 2 g/m$^2$ can be used to accommodate patients who are less fit. The role of autologous HCT in the intermediate-risk group outside of clinical trials is diminishing due to improvements in allogeneic transplants, which are expanding the pool of potential donors outside the family setting. While autologous HCT is still incorporated into the clinical trial design in Europe, the consensus of the NCCN AML Panel was that autologous HCT should not be a recommended consolidation therapy outside the setting of a clinical trial. Clinical trial participation is encouraged. Another option for this group includes multiple courses (3–4) of HiDAC consolidation.[253] If patients decline or are not fit/eligible for allogeneic HCT, maintenance therapy with oral azacitidine may be considered at 300 mg daily on days 1–14 of each 28-day cycle until disease progression or unacceptable toxicity (a category 2B option).[251] The panel notes that this option is not intended to replace consolidation chemotherapy.

HiDAC (1.5–3 g/m$^2$) with midostaurin may be considered for patients with *FLT3*-mutation–positive AML.[254] Alternative regimens incorporating intermediate doses of cytarabine may be reasonable in patients with intermediate-risk disease, including intermediate-dose cytarabine (1000 mg/m$^2$) plus daunorubicin and GO for patients with CD33-positive AML.[214] However, the panel notes that patients who receive a transplant shortly following GO administration may be at risk for developing sinusoidal obstruction syndrome.[255] If a transplant is planned, prior studies have used a 60- to 90-day interval between the last administration GO and stem cell transplant.[214] Comparable 5-year DFS rates were reported in patients younger than 60 years with NK-AML after either 4 cycles of intermediate-dose cytarabine or HiDAC (41%) or autologous HCT (45%).[253] At this time, there is no evidence that HiDAC (2–3 g/m$^2$) is superior to intermediate-dose cytarabine in patients with intermediate-risk AML.

#### *Treatment-Related Disease Other than CBF and/or Unfavorable Cytogenetics and/or Molecular Abnormalities*

The panel strongly recommends clinical trials as standard therapy for patients with poor prognostic features, which include *FLT3*-ITD abnormalities in the setting of otherwise NK-AML, high WBC (>50,000/mcL) at diagnosis, or adverse cytogenetics/molecular markers as well as secondary and therapy-related AML. If remission is observed, consolidation therapy is recommended, and strong consideration should be given to allogeneic HCT with matched sibling or alternative donor (including umbilical cord blood products) as part of consolidation strategy. HiDAC-based consolidation with or without midostaurin for *FLT3*-mutation–positive AML (as outlined for patients with intermediate-risk AML) may be required to maintain remission while searching for a potential matched donor. If CPX-351 was given during induction, an additional treatment of CPX-351 [cytarabine (65 mg/m$^2$) and daunorubicin (29 mg/m$^2$)] as an intravenous infusion over 90 minutes on days 1 and 3 for 1 cycle is recommended for patients with therapy-related AML other than CBF/APL, antecedent MDS/CMML, or AML-MRC.[229] If patients decline or are not fit/eligible for allogeneic HCT, maintenance therapy with oral azacitidine may be considered at 300 mg daily on days 1–14 of each 28-day cycle until disease progression or unacceptable toxicity.[251] As previously stated, the panel notes that this option is not intended to replace consolidation chemotherapy.

### Management of AML in Patients >60 Years

#### *Induction Therapy*

The creation of separate guidelines for patients >60 years recognizes the poor outcomes in this group treated with standard cytarabine and an anthracycline. In patients >60 years, the proportion of those with favorable CBF translocations decreases, as does the number with isolated *NPM1* mutations, whereas the number of patients with unfavorable karyotypes and mutations increases. However, it should be noted that although some studies have demonstrated that *NPM1* mutations in patients who are older is a positive prognostic factor,[256,257] other emerging studies suggest it may predict unfavorable outcomes.[258,259] In the UK NCRI AML 16 trial, similar to younger patients, in patients who are older, only the combined wild-type *FLT3* and *NPM1* mutant group had improved survival.[256] This same study also demonstrated that the *FLT3* mutation did not affect remission rates, though there was an association with inferior survival. Secondary AML, either related to prior MDS or prior chemotherapy, also increases along with a higher rate of multidrug resistance protein expression. Although studies in the Swedish Acute Leukemia Registry documented improvement in outcomes for patients younger than 60 years over the past 3 decades, no similar improvement was observed for the population >60 years.[206,260] Treatment-related mortality frequently exceeds any expected transient response in this group, particularly in patients >75 years or in those who have significant comorbid conditions or ECOG performance status greater than 2.

For patients >60 years with AML, the panel recommends using patient performance status, in addition to adverse features (eg, *de novo* AML without favorable cytogenetics or molecular markers; therapy-related AML; antecedent hematologic disorder) and comorbid conditions, to select treatment options rather than rely on a patient's chronologic age alone. Comprehensive geriatric assessments are complementary to assessment of comorbid conditions and are emerging as better predictive tools of functional status.[261,262] A treatment decision-making algorithm for previously untreated, medically fit, patients ≥60 years with AML was developed by the German AML cooperative group. Based on data from a large study in patients ≥60 years (n = 1406), patient and disease factors significantly associated with CR and/or early death were identified and risk scores were developed based on multivariate regression analysis.[263] The predictive model was subsequently validated in an independent cohort of patients ≥60 years (n = 801) treated with 2 courses of induction therapy with cytarabine and daunorubicin. The algorithm, with or without knowledge of cytogenetic or molecular risk factors, predicts the probability of achieving a CR and the risk for an early death for elderly patients with untreated AML who are medically fit and therefore considered eligible for standard treatments.[263] The factors included in the algorithm are the following: body temperature (≤38°C and >38 °C), hemoglobin levels (≤10.3 and >10.3 g/dL), platelet counts (≤28K, >28K–≤53K, >53K–≤104K, and >104K counts/mcL), fibrinogen levels (≤150 and >150 mg/dL), age at diagnosis (60–64, >64–67, >67–72, and >72 years), and type of leukemia (de novo and secondary). The algorithm can be accessed online at http://www.aml-score.org/.

A comprehensive predictive model for early death following induction in patients with newly diagnosed AML suggests that age may reflect other covariants, and the evaluation of these factors may provide a more accurate predictive model. The model includes performance score, age, platelet count, serum albumin, presence or absence of secondary AML, WBC count, peripheral blood blast percentage, and serum creatinine. These factors, when taken together, result in a predictive accuracy based on the area under the curve (AUC) of 0.82 (a perfect correlation is an AUC of 1.0).[264] This model is complex, and currently there is not a tool available to implement this model. A shortened form of the model was based on covariants that include age, PS, and platelet count. The simplified model provides an AUC of 0.71, which is less accurate than the complex model but may be more accurate than decision-making strategies based solely on age.[264] Based on this model, a Treatment Related Mortality calculator can be accessed online at https://www.fhcrc-research.org/TRM/Default.aspx?GUID=1358501B-C922-4422-84F0-0E6C67D8F266.

In a retrospective cohort study of adult patients with AML (n = 1100; range, 20–89 years), a composite predictive model examined the impact of comorbidities on 1-year mortality following induction treatment.[265] This analysis incorporated patient-specific (ie, age, comorbidities) and AML-specific (ie, cytogenetic and molecular risks) features, and resulted in a predictive estimate of 0.76 based on AUC.[265] This model can be accessed online at http://www.amlcompositemodel.org/.

Adults who are older with intact functional status (ie, ECOG score 0–2), minimal comorbidity, and *de novo* AML without unfavorable cytogenetics or molecular markers, without antecedent hematologic disorder, and without therapy-related AML may benefit from intensive cytarabine-based therapy regardless of chronologic age.

***Candidates for Intensive Remission Induction Therapy***

***Favorable- or Intermediate-Risk Cytogenetics***

A reasonable treatment regimen for patients with favorable- or intermediate-risk cytogenetics includes standard-dose cytarabine (100–200 mg/m$^2$ by continuous infusion per day for 7 days) along with 3 days of anthracycline. Although patients >75 years with significant comorbidities

generally do not benefit from conventional chemotherapy treatment, the rare patient with favorable-risk or NK-AML and no significant comorbidities might be the exception to this dogma. For patients with NK-AML, the remission rates are 40% to 50% with cytarabine combined with idarubicin, daunorubicin, or mitoxantrone. The randomized study from the Acute Leukemia French Association (ALFA)-9801 study (n = 468) showed that idarubicin induction (the standard 12 mg/m$^2$ daily for 3 days or intensified with 12 mg/m$^2$ daily for 4 days) compared with high-dose daunorubicin (up to 80 mg/m$^2$) yielded a significantly higher CR rate in patients aged 50 to 70 years (80% vs. 70%, respectively; *P* = .03).[209] The median OS for all patients was 17 months. The estimated 2-year EFS and OS rates were 23.5% and 38%, respectively, and the estimated 4-year EFS and OS rates were 18% and 26.5%, respectively; however, no significant differences were observed between treatment arms with regard to EFS, OS, and cumulative relapse rates.[209]

The ALFA-9803 study (n = 416) evaluated (during first randomization) induction with idarubicin (9 mg/m$^2$ daily for 4 days) compared with daunorubicin (45 mg/m$^2$ daily for 4 days) in patients ≥65 years.[266] In this trial, the CR rate after induction was 57% and induction death occurred in 10% of patients. The median OS for all patients was 12 months; the estimated 2-year OS rate was 27%. No significant differences in these outcomes were seen between anthracycline treatment arms.[266] Long-term outcomes based on a combined analysis of data from the two ALFA trials above (9801 and 9803 studies; n = 727) showed superior results with standard idarubicin induction (36 mg/m$^2$ total dose) compared with daunorubicin induction (240 mg/m$^2$ total dose for patients <65 years; 180 mg/m$^2$ total dose for patients ≥65 years) in patients ≥50 years with AML.[267] At a median actuarial follow-up of 7.5 years, the median OS for all patients included in the analysis was 14.2 months. The estimated 5-year OS rate was 15.3%, and the overall cure rate was 13.3%. Induction with standard idarubicin was associated with a significantly higher cure rate compared with daunorubicin (16.6% vs. 9.8%; *P* = .018). In the group of patients younger than age 65 years, standard idarubicin was still associated with a significantly higher cure rate than daunorubicin despite the high dose (240 mg/m$^2$ total dose) of daunorubicin (27.4% vs. 15.9%; *P* = .049).[267]

In the HOVON trial, which randomized patients ≥60 years to induction therapy with standard-dose cytarabine combined with either standard-dose daunorubicin (45 mg/m$^2$ daily for 3 days; n = 411) or dose-escalated daunorubicin (90 mg/m$^2$ daily for 3 days; n = 402), the CR rate was 54% and 64%, respectively (*P* = .002).[268] No significant differences were observed in EFS, DFS, or OS outcomes between treatment arms. Among the subgroup of patients aged 60 to 65 years (n = 299), an advantage with dose-escalated compared with standard-dose daunorubicin was observed with regard to rates of CR (73% vs. 51%), 2-year EFS (29% vs. 14%), and 2-year OS (38% vs. 23%). These outcomes with dose-escalated daunorubicin seemed similar to those with idarubicin (12 mg/m$^2$ daily for 3 days) from the ALFA-9801 study, in which the 4-year EFS and OS rates were 21% and 32%, respectively.[209] In the HOVON trial, the benefit in OS outcomes for the dose-escalated daunorubicin group was observed only in patients aged 65 years and younger or in those with CBF translocations.[268]

For patients who exceed anthracycline dose or have cardiac issues but are still able to receive intensive therapy, alternative non–anthracycline-containing regimens, including clofarabine, may be considered.[269-273]

***CD33-Positive AML:*** There are conflicting data about the use of GO for patients who are older with AML. Three phase III randomized trials evaluated the efficacy and safety of adding the anti-CD33 antibody-drug conjugate GO to induction therapy with daunorubicin and cytarabine in patients who are older with previously untreated AML.[274-276] In the phase III ALFA-0701 trial, patients aged 50 to 70 years with *de novo* AML (n = 280) were randomized to receive induction with daunorubicin (60 mg/m$^2$ daily

for 3 days) and cytarabine (200 mg/m$^2$ continuous infusion for 7 days), with or without (control arm) fractionated GO 3 mg/m$^2$ given on days 1, 4, and 7.[276] Patients with persistent marrow blasts at day 15 received additional daunorubicin and cytarabine. Patients who achieved a CR/CRi after induction received two consolidation courses with daunorubicin and cytarabine, with or without GO (3 mg/m$^2$ on day 1). The CR/CRi after induction was similar between the GO and control arms (81% vs. 75%). The GO arm was associated with significantly higher estimated 2-year EFS (41% vs. 17%; *P* = .0003), RFS (50% vs. 23%; *P* = .0003), and OS (53% vs. 42%; *P* = .0368) rates compared with the control.[276] The GO arm was associated with a higher incidence of hematologic toxicity (16% vs. 3%; *P* < .0001); this was not associated with an increase in the risk of death from toxicity.[276]

In another multicenter, phase III, randomized trial from the UK and Denmark (AML-16 trial), patients >50 years with previously untreated AML or high-risk MDS (n = 1115) were randomized to receive daunorubicin-based induction (daunorubicin combined with cytarabine or clofarabine) with or without (control) GO (3 mg/m$^2$ on day 1 of course 1 of induction).[275] The median age was 67 years (range, 51–84 years) and 98% of patients were ≥60 years; 31% were ≥70 years. The CR/CRi rate after induction was similar between the GO and control arms (70% vs. 68%). The GO arm was associated with significantly lower 3-year cumulative incidence of relapse (68% vs. 76%; *P* = .007) and higher 3-year RFS (21% vs. 16%; *P* = .04) and OS (25% vs. 20%; *P* = .05) rates compared with the control arm. The early mortality rates were not different between treatment arms (30-day mortality rate, 9% vs. 8%); in addition, no major increase in adverse events was observed with GO.[275] These two trials suggest that the addition of GO to standard induction regimens reduced the risk of relapse and improved OS outcomes in patients who are older with previously untreated AML characterized by favorable or intermediate-risk cytogenetics, not adverse risk.

The third phase III trial combining GO with chemotherapy showed a different result than the other two. In this study, patients between the ages of 61 and 75 years were given chemotherapy consisting of mitoxantrone, cytarabine, and etoposide (n = 472).[274] Half of the patients were given 6 mg/m$^2$ GO prior to chemotherapy on days 1 and 15. In remission, treatment included two courses of consolidation with or without 3 mg/m$^2$ GO on day 0. The OS between the two groups was similar (GO, 45% vs. no GO, 49%), but the induction and 60-day mortality rates were higher in the patients given GO (17% vs. 12% and 22% vs. 18%, respectively). Only a small subgroup of patients younger than 70 years of age with secondary AML showed any benefit to treatment. Combined with the increased toxicity, the results of this study suggest that GO may not provide an advantage over standard chemotherapy for some patients who are older with AML.[274]

Conflicting studies have led to the publication of several systematic reviews and meta-analyses. A larger systematic review, inclusive of any RCTs that investigated the benefit of anti-CD33 antibody therapy, regardless of whether treatment was in de novo or secondary disease, concluded that the data from 11 trials showed increased induction deaths (*P* = .02) and reduced residual disease (*P* = .0009).[277] Despite improved RFS (HR, 0.90; 95% CI, 0.84–0.98; *P* = .01), no OS benefit was measured (HR, 0.96; 95% CI, 0.90–1.02; *P* = .2). Two other meta-analyses showed improved RFS, though induction death was elevated.[278,279] Conversely, a fourth meta-analysis evaluating 5 trials with 3325 patients ≥15 years showed a reduced risk of relapse (*P* = .0001) and improved 5-year OS (OR, 0.90; 95% CI, 0.82–0.98; *P* = .01) with the addition of GO to conventional induction therapy.[215] It was noted that the greatest survival benefit was seen in patients with favorable cytogenetics. Some benefit was seen in patients with intermediate cytogenetics, but no benefit was reported with the addition of GO in patients with adverse cytogenetics.

These studies underscore the need for further investigation that elucidates the benefits of GO for the treatment of AML.

***FLT3-Positive AML:*** The results of the CALGB 10603/RATIFY Alliance trial[221] have been described in an earlier section (See *Management of AML in Patients Younger Than 60 Years; Intermediate-Risk Cytogenetics*) and these data may be extrapolated to suggest benefit in fit adults who are older. In a phase II study in adult patients with previously untreated AML (n = 284; range, 18–70 years; 86 patients included between the ages of 61–70 years), the efficacy and safety of midostaurin added to intensive chemotherapy, followed by allogeneic HCT and single-agent midostaurin maintenance therapy for a year was evaluated.[280] All patients were confirmed to have *FLT3*-ITD–positive disease. The CR/CRi rate after induction therapy was 76.4% (age <60 years, 75.8%; age >60 years, 77.9%). Many patients proceeded to transplant (72.4%), and a subset initiated maintenance therapy (n = 97; 75 after allogeneic HCT and 22 after HiDAC consolidation). The median time receiving maintenance therapy was 9 months after allogeneic HCT and 10.5 months after HiDAC consolidation. The 2-year EFS and OS rates were 39% and 34% in patients <60 years, and 53% and 46% in patients >60 years.[280]

***Therapy-Related AML or Antecedent MDS/CMML or AML-MRC***

The studies evaluating the efficacy and safety of CPX-351 in patients aged 60 to 75 years with newly diagnosed secondary AML have been described (*Management of AML in Patients Younger Than 60 Years; Therapy-Related AML or Antecedent MDS/CMML or AML-MRC).*[229]

***Unfavorable-Risk Cytogenetics (exclusive of AML-MRC)***

***Hypomethylating Agents (HMAs):*** An international, randomized, phase III study by Fenaux et al[281] compared the HMA 5-azacitidine with conventional care (best supportive care, low-dose cytarabine, or intensive chemotherapy) in patients with MDS (n = 358). Although this study was designed for evaluation of treatment in patients with high-risk MDS (based on FAB criteria), 113 study patients (32%) fulfilled criteria for AML using the 2008 WHO classification, with marrow-blast percentages between 20% and 30%.[281,282] In the subgroup of these patients with AML, a significant survival benefit was found with 5-azacitidine compared with conventional care regimens, with a median OS of 24.5 months versus 16 months (HR, 0.47; 95% CI, 0.28–0.79; *P* = .005).[282] The 2-year OS rates were 50% and 16%, respectively (*P* = .001). In a phase III study focused on adult patients ≥65 years, the efficacy and safety of azacitidine versus conventional care regimens (standard induction chemotherapy, low-dose cytarabine, or supportive care) was evaluated in patients with newly diagnosed AML with >30% blasts.[283] Compared to conventional care regimens, azacitidine was associated with an increase in median OS (6.5 months vs.10.4 months; HR, 0.85; 95% CI, 0.69–1.03; stratified log-rank *P* = .1009).[283] The 1-year survival rates with azacitidine and conventional care regimens were 46.5% and 34.2%, respectively.

Another HMA, decitabine, has also been evaluated as remission induction therapy for patients who are older with AML.[284] In a phase II study in previously untreated patients ≥60 years (n = 55; median age, 74 years), the overall CR rate with this agent (20 mg/m$^2$ for 5 days every 28 days) was 24% (including 6 out of 25 patients [24%] with poor-risk cytogenetics), and the median EFS and OS were 6 months and 8 months, respectively.[284] An earlier phase I study evaluated different dose schedules of decitabine in patients with R/R leukemias (n = 50; AML diagnosis, n = 37).[285] In this study decitabine was given at 5, 10, 15, or 20 mg/m$^2$ for 5 days per week for 2 to 4 consecutive weeks (ie, 10, 15, or 20 days). The decitabine dose of 15 mg/m$^2$ for 10 days (n = 17) was associated with the highest response rates, with an overall response rate (ORR) of 65% and CR rate of 35%. Among the patients with R/R AML (n = 37), the ORR was 22% with a CR in 14% across all dose levels.[285] A phase II study targeting patients ≥60 years with AML who were not candidates for or declined intensive therapy, administered a decitabine

dose of 20 mg/m$^2$ for 10 days and demonstrated a CR rate of 47% (n = 25) after a median of three cycles of therapy.[286] In a study aimed at identifying the relationship between molecular markers and clinical responses to decitabine, adult patients with AML and MDS (n = 116; median age, 74 years; range, 29–88 years) were treated with decitabine (20 mg/m$^2$ for 10 days every 28 days).[287] Response rates were higher among patients with unfavorable-risk cytogenetics compared to patients with favorable- or intermediate-risk (67% vs. 34%, respectively; *P* < .001), and in the setting of *TP53* mutations compared to wild-type *TP53* (100% vs. 41%; *P* < .001).[287] A recent phase II study comparing a 5-day versus 10-day treatment schedule for decitabine in patients ≥60 years (n = 71) with newly diagnosed AML determined that the efficacy and safety of both schedules were not significantly different.[288]

In an open-label, randomized, phase III study, decitabine (20 mg/m$^2$ for 5 days every 28 days) was compared with physician's choice (either low-dose cytarabine [20 mg/m$^2$/day SC for 10 consecutive days every 28 days] or supportive care) in patients ≥65 years with newly diagnosed AML.[289] Based on the protocol-specified final analysis of the primary endpoint (OS), decitabine was associated with a statistically nonsignificant trend for increased median OS compared with physician's choice (7.7 months vs. 5 months; HR, 0.85; 95% CI, 0.69–1.04; *P* = .108). A subsequent post hoc analysis of OS with additional follow-up time showed the same median OS with a statistically significant advantage associated with decitabine (HR, 0.82; 95% CI, 0.68–0.99; *P* = .037). The CR (including CRi) rate was significantly higher with decitabine (18% vs. 8%; *P* = .001).[289] The most common treatment-related adverse events with decitabine versus cytarabine included thrombocytopenia (27% vs. 26%), neutropenia (24% vs. 15%), febrile neutropenia (21% vs. 15%), and anemia (21% vs. 20%). The 30-day mortality rates were similar between the decitabine and cytarabine groups (9% vs. 8%).[289] Both azacitidine and decitabine are approved by the FDA for the treatment of patients with MDS.

***Venetoclax-Containing Regimens:*** Emerging studies have evaluated the combination of HMAs with venetoclax, an oral B-cell lymphoma 2 (*BCL2*) inhibitor, as an induction therapy strategy for patients who are older with AML. In a phase Ib study, patients ≥65 years with previously untreated AML (n = 57) were enrolled into 3 groups: group A (n = 23) received venetoclax and decitabine (20 mg/m$^2$ daily for 5 days of each 28-day cycle); group B (n = 22) received venetoclax and azacitidine (75 mg/m$^2$ daily for 7 days of each 28-day cycle); and group C, a substudy of venetoclax and decitabine (n = 12), received an oral CYP3A inhibitor, posaconazole, to determine its effect on the pharmacokinetics of venetoclax.[290] Daily target doses for venetoclax in different cohorts within groups A and B were 400 mg, 800 mg, and 1200 mg. The most common treatment-related adverse event in groups A and B was febrile neutropenia (30% and 32%, respectively), with an overall CR/CRi rate of 61% (95% CI, 47.6–74.0).[290] In groups A and B, the CR/CRi rate was 60% (95% CI, 44.3–74.3).[290]

In a follow-up to this study, the efficacy of either 400 mg or 800 mg of venetoclax combined with either decitabine or azacitidine was evaluated in patients ≥65 years with previously untreated AML and who were ineligible for intensive chemotherapy (n = 145; median age, 74 years).[291] The venetoclax dose of 400 mg was found to be the recommended phase II dose. With a median time on study of 8.9 months (range, 0.2–31.7 months) and median duration of follow-up of 15.1 months (range, 9.8–31.7 months), 67% of patients achieved CR/CRi.[291] The median duration of CR/CRi and median OS was 11.3 months and 17.5 months, respectively.[291] In a subgroup analysis, the CR/CRi rates of patients with intermediate- and poor-risk cytogenetics were 74% and 60%, with a median duration of 12.9 months (95% CI, 11.0 months–NR) versus 6.7

months (95% CI, 4.1–9.4 months), respectively.[291] The CR/CRi rates in with the setting of *TP53*, *IDH1/2*, and *FLT3* mutations were 47%, 71%, and 72%, respectively. In addition, patients with *de novo* AML and secondary AML, respectively, had the same CR/CRi rate of 67%, with a median duration of CR/CRi of 9.4 months (95% CI, 7.2–11.7 months) versus not reached (NR) (95% CI, 12.5 months–NR).[291] In a phase 3 follow-up to this study, at a median follow-up of 20.5 months, the median OS was 14.7 months in the group treated with azacitidine and venetoclax and 9.6 months in the group treated with azacitidine only (control) (HR, 0.66; 95% CI, 0.52–0.85; *P* = .001).[292] The CR/CRi rate was also higher in the azacitidine and venetoclax group versus the control group (66.4% vs. 28.3%, respectively; *P* = .001).[292]

Another phase Ib/II study evaluated the efficacy of venetoclax combined with low-dose cytarabine (20 mg/m$^2$ daily for 10 days) in patients ≥60 years with previously untreated AML ineligible for intensive chemotherapy (n = 82; median age, 74 years).[293] All patients received at least one dose of venetoclax at 600 mg. The CR/CRi rate was 54% (95% CI, 42%–65%) with a median duration of remission of 8.1 months (95% CI, 5.3–14.9 months), and the median OS for all patients was 10.1 months (95% CI, 5.7–14.2 months).[293] Patients with *de novo* AML, intermediate-risk cytogenetic features, and no prior HMA exposure demonstrated CR/CRi rates of 71%, 63%, and 62%, respectively.[293] The average CR/CRi rates in the setting of *NPM1* or *IDH1/2* mutations were higher than in the setting of *TP53* or *FLT3* mutations (89% and 72% vs. 30% and 44%, respectively).[293] Based on these studies, venetoclax in combination with HMAs, decitabine or azacitidine, or low-dose cytarabine are approved by the FDA for the treatment of newly diagnosed AML in adults ≥75 years, or in patients who have comorbidities that preclude use of intensive induction chemotherapy.

***Not a Candidate for or Declines Intensive Remission Induction Therapy***

***AML Without Actionable Mutations***

In adult patients who are older who cannot tolerate intensive treatment strategies, low-intensity approaches have been investigated, including use of HMAs alone or combined with venetoclax (see *Candidates for Intensive Remission Induction Therapy, Hypomethylating Agents, and Venetoclax-Containing regimens* in the previous section).

***Low-Dose Cytarabine-Containing Regimens:*** Other approaches have evaluated low-dose cytarabine. The UK NCRI AML 14 trial randomized 217 patients primarily aged >60 years (*de novo* AML, n = 129; secondary AML, n = 58; high-risk MDS, n = 30) unfit for chemotherapy to receive either low-dose cytarabine subcutaneously (20 mg twice daily for 10 consecutive days, every 4–6 weeks) or hydroxyurea (given to maintain target WBC counts <10,000/mcL).[294] Patients were also randomized to receive ATRA or no ATRA. Low-dose cytarabine resulted in a CR rate of 18% (vs. 1% with hydroxyurea) and a survival benefit compared with hydroxyurea in patients with favorable or NK-AML. No advantage was observed with the addition of ATRA. The median DFS in patients who achieved a CR with low-dose cytarabine was 8 months.[294] Even with this "low-intensity" treatment approach, induction death occurred in 26% of patients, and overall prognosis remained poor for patients who are older who cannot tolerate intensive chemotherapy regimens. A phase II study evaluated a regimen with low-dose cytarabine (20 mg twice daily for 10 days) combined with clofarabine (20 mg/m$^2$ daily for 5 days) in patients ≥60 years with previously untreated AML (n = 60; median age, 70 years; range, 60–81 years).[295] Patients who experienced response received consolidation (up to 17 courses) with clofarabine plus low-dose cytarabine alternated with decitabine. Among evaluable patients (n = 59), the CR rate was 58% and median RFS was 14 months. The median OS for all patients was 12.7 months. The induction mortality rate was 7% at 8 weeks.[295] Although this regimen appeared to be active in patients ≥60 years with

AML, the authors noted that the benefits of prolonged consolidation remain unknown.

In a phase II trial, low-dose cytarabine was combined with glasdegib, a selective inhibitor of the Smoothened protein in the Hedgehog signaling pathway, and evaluated in adult patients (age ≥55 years) with previously untreated AML or high-risk MDS ineligible for intensive chemotherapy (n = 132).[296] Criteria for unsuitability for intensive chemotherapy included being ≥75 years of age, having serum creatinine >1.3 mg/dL, and having severe cardiac disease or ECOG score = 2. Patients were randomized 2:1 to receive low-dose cytarabine alone (20 mg twice daily for 10 days every 28 days) or combined with oral glasdegib (100 mg daily). The addition of glasdegib to low-dose cytarabine also improved OS compared to low-dose cytarabine alone (8.8 months vs. 4.9 months, respectively), and the CR rates were higher in the low-dose cytarabine and glasdegib arm (17%, n = 15/88) compared to low-dose cytarabine alone (2.3%; n = 1/44).[296] In the glasdegib plus low-dose cytarabine arm, the benefit in CR was primarily seen in patients with favorable-/intermediate-risk cytogenetics (n = 10/52) when compared to patients with poor risk cytogenetics (n = 5/36).[296] Glasdegib in combination with low-dose cytarabine is currently approved by the FDA for the treatment of newly diagnosed AML in adults ≥75 years, or in patients who have comorbidities that preclude use of intensive induction chemotherapy.

***CD33-Positive AML:*** Single-agent GO has also been evaluated as an option. A randomized phase III study evaluated the efficacy of single-agent GO (6 mg/m$^2$ on day 1 and 3 mg/m$^2$ on day 8) versus best supportive care as first-line therapy in patients ≥61 years with AML who were not eligible for intensive chemotherapy (n = 237).[297] Compared to best supportive care, GO alone improved the 1-year OS rate (9.7% vs. 24.3%, respectively). In the GO group, the median OS was 4.9 months (95% CI, 4.2–6.8 months) and 3.6 months (95% CI, 2.6–4.2 months) in the best supportive care group.[297]

***IDH Mutation-Positive AML:*** Initially approved by the FDA for use in the R/R AML setting, *IDH*-targeted inhibitors, enasidenib and ivosidenib, have demonstrated utility in the frontline setting.[298,299] In a phase I/II study, the clinical activity and safety of enasidenib, an *IDH2* mutant inhibitor, was evaluated in adult patients with *IDH2*-mutated advanced AML including R/R disease.[300] Approximately 19% of patients (n = 34 of 176) with R/R AML achieved complete remission, with an OS of 19.7 months with a median OS of 9.3 months.[300] In patients ≥60 years with newly diagnosed AML, the efficacy of enasidenib was evaluated in a phase Ib/II sub-study within the Beat AML trial.[299] Patients were treated with enasidenib (100 mg/day) in continuous 28-day cycles. Azacitidine (75 mg/m$^2$ days 1–7) was added to enasidenib for some patients who did not achieve CR/CRi by cycle 5. Of 23 evaluable patients receiving enasidenib monotherapy, CR/CRi was achieved in 43% of patients (7 CR/2 CRi).[299]

Ivosidenib, an *IDH1*-mutation inhibitor, demonstrated durable remissions in *IDH1* R/R AML, with 30.2% of patients (n = 54 of 179) with R/R AML achieving CR/CRh.[301] As an extension of this study, the safety and efficacy of ivosidenib in patients with untreated AML was evaluated (n = 34; median age, 76.5 years).[298] In phase I dose-escalation and expansion, patients received ivosidenib once daily or twice daily in 28-day cycles, and a dose of 500 mg per day was selected as the dose for expansion groups. The CR/CRh rate was 41.2% (95% CI, 24.6%–59.3%), and the ORR was 58.8% (20/34; 95% CI, 40.7%–75.4%).[298] Based on these data, ivosidenib was approved by the FDA in May 2019 as a first-line treatment option for AML with an *IDH1* mutation in patients who are ≥75 years or who have comorbidities that preclude the use of intensive induction chemotherapy. Treatment with both enasidenib and ivosidenib may induce differentiation

syndrome and hyperleukocytosis, which may be managed with corticosteroids and hydroxyurea.[302-304]

Alternatively, emerging data suggest that patients with *de novo* AML characterized by *IDH1/2*-mutant AML may benefit from venetoclax/HMA-based therapy with reported remission rates of greater than 70%, albeit in a relatively small number of patients.[291]

***FLT3-Positive AML:*** In adult patients with newly diagnosed *FLT3*-mutation-positive AML (n = 15; median age, 76 years; range, 65–86 years), an ongoing trial is evaluating the safety and tolerability of the combination of azacitidine and gilteritinib,[305] a *FLT3* inhibitor that has demonstrated antileukemic activity in *FLT3*-positive R/R AML.[306,307] Of 15 evaluable patients, a CR/CRi rate of 67% was observed.[305] Another study evaluated the efficacy of azacitidine and sorafenib, a *FLT3* inhibitor, as a front-line strategy in adult patients ≥60 years with *FLT3*-ITD mutation-positive AML who cannot tolerate intensive induction (n = 27; median age, 74 years; range, 61–86 years).[308] The ORR was 78%, with CR, CRi/CR with incomplete platelet recovery (CRp), and PR rates of 26%, 44%, and 7%, respectively.[308] In addition, the median duration of CR/CRi/CRp was 14.5 months, with a median OS of 8.3 months for the whole group.[308]

***NCCN Recommendations***

Similar to recommendations for adults younger than 60 years, the NCCN AML Panel encourages enrollment in a clinical trial for treatment induction of patients aged ≥60 years with AML. For patients not enrolled in a clinical trial, cytogenetics, overall functional status, and the presence or absence of actionable mutations should guide treatment strategies.

***Candidates for Intensive Remission Induction Therapy:*** Standard infusional cytarabine and anthracycline is recommended. For patients who exceed anthracycline dose guidelines or have cardiac issues but who are still fit enough to receive aggressive therapy, alternative non-anthracycline–containing regimens may be considered. Gemtuzumab ozogamicin (GO) may be added to standard-dose cytarabine combined with daunorubicin for patients with CD33-positive AML and who have favorable- or intermediate-risk cytogenetics. Midostaurin is added to standard-dose cytarabine combined with daunorubicin for patients with *FLT3*-mutated AML. For patients with therapy-related AML, antecedent hematologic disorder, or AML-MRC, treatment with CPX-351 [cytarabine (100 mg/m$^2$) and daunorubicin (44 mg/m$^2$)] as intravenous infusion over 90 minutes on days 1, 3, and 5 of 1 cycle is recommended (a category 1 recommendation).

For patients with unfavorable-risk cytogenetics exclusive of AML-MRC, recommended options include: venetoclax combined with azacitidine, decitabine or low-dose cytarabine, or lower-intensity therapy with HMAs (5-azacitidine [a category 2B recommendation] or decitabine).

***Not a Candidate for or Declines Intensive Remission Induction Therapy:*** Treatment options include a clinical trial, or lower-intensity therapy based on the presence or absence of actionable mutations. The preferred regimens include venetoclax combined with HMAs (azacitidine [category 1] or decitabine). Other recommended options include venetoclax combined with low-dose cytarabine [LDAC] or glasdegib combined with LDAC. Patients not considered candidates for combination or targeted therapy may receive monotherapy with HMA (azacitidine or decitabine for either a 5- or 10-day course), GO alone (a category 2B recommendation), or LDAC alone (a category 3 recommendation). Best supportive care with hydroxyurea and transfusion support should also be considered and have been used as the comparator arm in several clinical trials in unfit patients who are older.

For patients with *IDH1*- or *IDH2*-mutant AML, preferred treatment options include: ivosidenib or enasidenib for *IDH1*- or *IDH2*-mutant AML respectively; or venetoclax-based therapy combined with HMAs

(azacitidine [category 1] or decitabine). Other recommended options include venetoclax combined with LDAC or low-intensity therapy with HMAs (azacitidine or decitabine). For patients with *FLT3*-mutant AML, the preferred treatment option is also venetoclax-based therapy combined with HMAs (azacitidine [category 1] or decitabine). Other treatment options for this category include HMAs in combination with sorafenib and venetoclax combined with LDAC.

***Postinduction Therapy***

***After Standard-Dose Cytarabine Induction***

Similar to younger patients, patients ≥60 years who receive standard cytarabine/anthracycline induction with or without midostaurin or GO, or a dual-drug encapsulation of cytarabine and daunorubicin receive a bone marrow evaluation 14 to 21 days after start of therapy and are categorized according to the presence of blasts or hypoplasia. Patients with hypoplasia should await recovery of counts before continuing to post-remission therapy. Patients with residual disease without hypoplasia may receive additional standard-dose cytarabine with an anthracycline or mitoxantrone, or CPX-351 [cytarabine (100 mg/m$^2$) and daunorubicin (44 mg/m$^2$)], if given during induction for patients with therapy-related AML, antecedent hematologic disorder, or AML-MRC. Alternatively, patients with *FLT3*-mutation–positive AML may receive additional standard-dose cytarabine with daunorubicin and midostaurin. Additional treatment strategies for these patients may include consideration of a clinical trial or use of regimens used for R/R disease (see *Management of Relapsed/Refractory AML*).

If daunorubicin (90 mg/m$^2$) was used in induction, the recommended dose for reinduction prior to count recovery is 45 mg/m$^2$ for no more than 2 doses. Similarly, if idarubicin (12 mg/m$^2$) was used for induction, the early reinduction dose should be limited to 10 mg/m$^2$ for 1 or 2 doses. Intermediate-dose cytarabine-containing regimens, allogeneic HCT, or best supportive care are also treatment options. Allogeneic transplant is a reasonable option, preferably in the context of a clinical trial, in patients who experience re-induction failure with certain regimens including intermediate-dose or HiDAC-containing regimens, and who have identified donors available to start conditioning within 4 to 6 weeks from start of induction therapy. Patients without an identified donor would most likely need some additional therapy as a bridge to transplant. Additionally, it is acceptable to await recovery in these patients as many will enter remission without further treatment. Regardless of treatment, all patients receiving post-induction therapy after standard-dose cytarabine should have a repeat bone marrow evaluation to document remission status. Because many patients who are older have some evidence of antecedent myelodysplasia, full normalization of peripheral blood counts often does not occur even if therapy clears the marrow blasts. Thus, many phase I/II trials for AML in patients who are older include categories such as CRi for patients who have fewer than 5% marrow blasts but mild residual cytopenias.

Many treatment strategies are designed to work more gradually using agents that may allow expression of tumor suppressor genes (eg, a methyltransferase inhibitor such as decitabine or 5-azacitidine) or increase apoptosis (eg, histone deacetylase inhibitors). Thus, success in these trials may be assessed using indirect measures, such as hematologic improvement or decreased transfusion requirements and survival, without actually achieving CR. Frequently, in these trials, marrow examination is not performed until completion of 1 to 2 cycles of therapy. However, the Guidelines do not currently recommend post-induction HMAs. For patients with residual disease after 1 cycle of induction chemotherapy who will not tolerate another intensive salvage, venetoclax-based regimens may be considered.[309,310]

***Postremission or Consolidation Therapy***

Patients who achieve a CR (including CRi) with standard induction chemotherapy may receive further consolidation with these same agents.

***Intermediate-Dose Cytarabine:*** The prospective CALGB trial[234] established the efficacy of HiDAC consolidation in patients with AML aged 60 years or younger.[234] In this study, a subgroup of patients with AML ≥60 years who received standard-dose cytarabine-daunorubicin induction therapy and more than one course of HiDAC consolidation (3 g/m$^2$ every 12 hours on days 1, 3, and 5, per course) experienced severe neurotoxicity and a 4-year DFS rate of less than 16%.[234] Although the CALGB trial did not show an overall benefit for higher doses of cytarabine consolidation in patients ≥60 years,[234] a subset of patients with a good performance status, normal renal function, and a normal or low-risk karyotype might be considered for a single cycle of cytarabine (1.0–1.5 g/m$^2$ daily for 4–6 doses) without an anthracycline. In a study by Sperr et al, the CALGB consolidation was modified and given as intermediate-dose cytarabine at 1 g/m$^2$ every 12 hours on days 1, 3, and 5, per course for 4 cycles in a group of patients >60 years with AML.[311] In this study, the treatment was well-tolerated without neurotoxicity and 25 of 47 patients received all 4 consolidation cycles. The median OS, DFS, and continuous CR were 10.6, 15.5, and 15.9 months, respectively.[311] The probability of OS, DFS, and continuous CR at 5 years were 18%, 22%, and 30%, respectively.[311]

***Allogeneic Hematopoietic Transplantation:*** The role of myeloablative allogeneic HCT is limited in patients who are older because of significant comorbidities; however, ongoing interest has been shown in RIC allogeneic HCT as consolidation therapy.[312,313] Case series and analysis of registry data have reported encouraging results, with 40% to 60% 2-year OS rates and 20% non-relapse mortality for patients who underwent transplant in remission.[312,313] In a retrospective analysis comparing outcomes with RIC allogeneic HCT and autologous HCT in patients ≥50 years based on large registry data, RIC allogeneic HCT was associated with lower risk for relapse and superior DFS and OS relative to autologous HCT.[312] The authors also noted that a survival benefit was not observed in the subgroup of patients undergoing RIC allogeneic HCT in first CR because of an increased incidence of non-relapse mortality.

Estey et al[314] prospectively evaluated a protocol in which patients ≥50 years with unfavorable cytogenetics would be evaluated for a RIC allogeneic HCT.[314] Of the 259 initial patients, 99 experienced a CR and were therefore eligible for HCT evaluation. Of these patients, only 14 ultimately underwent transplantation because of illness, lack of donor, declining transplantation, or unspecified reasons. The authors compared the results of RIC allogeneic HCT with those from matched subjects receiving conventional-dose chemotherapy. This analysis suggested that RIC allogeneic HCT was associated with improved RFS, and the authors concluded that this approach remains of interest.[314] In an analysis of outcomes between two different strategies for matched-sibling allogeneic HCT, outcomes in younger patients (aged ≤50 years; n = 35) receiving conventional myeloablative allogeneic HCT were compared with those in patients >50 years (n = 39) receiving RIC allogeneic HCT.[315] This study showed similar rates of 4-year non-relapse mortality (19% and 20%, respectively), and no difference was seen in relapse and OS rates.[315]

A retrospective study based on data in patients aged 50–70 years with AML compared outcomes in patients who underwent allogeneic HCT (either myeloablative conditioning or RIC; n = 152) with those who did not receive HCT in first CR (chemotherapy only; n = 884).[316] Allogeneic HCT in first CR was associated with a significantly lower 3-year cumulative relapse rate (22% vs. 62%; $P < .001$) and a higher 3-year RFS rate (56% vs. 29%; $P < .001$) compared with the non-HCT group. Although HCT was associated with a significantly higher rate of non-relapse mortality (21%

vs. 3%; *P* < .001), the 3-year OS rate showed a survival benefit with HCT (62% vs. 51%; *P* = .012).[316] Among the patients who underwent allogeneic HCT, myeloablative conditioning was used in 37% of patients, whereas RIC was used in 61%. Survival outcomes between these groups were similar, with 3-year OS rates of 63% and 61%, respectively.[316]

Another study evaluating treatment in patients aged 60–70 years compared outcomes between RIC allogeneic HCT reported to the Center for International Blood and Marrow Transplant Research (n = 94) and standard chemotherapy induction and postremission therapy from the CALGB studies (n = 96).[317] Allogeneic HCT in first CR was associated with significantly lower 3-year relapse (32% vs. 81%; *P* < .001) and higher 3-year leukemia-free survival rates (32% vs. 15%; *P* < .001) compared with the chemotherapy-only group. As would be expected, allogeneic HCT was associated with a significantly higher rate of non-relapse mortality (36% vs. 4%; *P* < .001) at 3 years; the 3-year OS rate was not significantly different between the groups (37% vs. 25%; *P* = .08), although there was a trend favoring allogeneic HCT.[317] A prospective multicenter phase II study examined the efficacy of RIC allogeneic HCT in patients aged 60–74 years with AML in first CR (n = 114).[318] After allogeneic HCT, DFS and OS at 2 years were 42% (95% CI, 33%–52%) and 48% (95% CI, 39%–58%), respectively, for the entire group.[318] A time-dependent analysis of four successive prospective HOVON-SAKK AML trials examined data from patients ≥60 years who obtained a first CR after induction chemotherapy (n = 640).[319] For patients who received allogeneic HCT as post-remission therapy (n = 97), a 5-year OS rate was 35% (95% CI, 25%–44%).[319]

Collectively, these studies suggest that RIC allogeneic HCT is a feasible treatment option for patients ≥60 years, particularly those in first CR with minimal comorbidities and who have an available donor. For this strategy to be better used, potential transplant options should be considered during induction therapy, and alternative donor options/searches should be explored earlier in the disease management. The guidelines note that RIC allogeneic HCT is considered an additional option for patients ≥60 years as postremission therapy in those experiencing a CR to induction therapy.

***Maintenance Therapy***

***Hypomethylating Agents:*** Preventing relapse in patients who are older with AML who have experienced first CR after intensive induction can be challenging. In a phase 3 randomized trial, HOVON97, investigators evaluated the efficacy of maintenance therapy with azacitidine in patients ≥60 years with AML or MDS with refractory anemia with excess of blasts (n = 116) who achieved CR or CRi after intensive chemotherapy.[320] Patients were randomized to either observation (n = 60) or treated with azacitidine (n = 56) at 50 mg/m$^2$ subcutaneously on days 1–5 every 4 weeks until relapse for a maximum of 12 cycles.[320] Thirty-five patients received at least 12 cycles of azacitidine and the estimated 12-month DFS for the azacitidine and observation groups were 64% and 42%, respectively (log rank, *P* = .04).[320]

The studies evaluating the efficacy and safety of maintenance therapy with oral azacitidine or CC-486 in patients with newly diagnosed AML who have experienced first CR or CRi but are unable to continue with conventional consolidation have been described (See *Management of AML in Patients Younger Than 60 Years*; sub-section: *Maintenance Therapy*).[248,251]

***NCCN Recommendations***

***Previous Intensive Therapy:*** For patients who had previously received intensive therapy, a marrow to document remission status upon hematologic recovery should be performed after 4 to 6 weeks. If a CR is observed, a clinical trial is recommended. Other postremission or maintenance therapy recommendations include: allogeneic HCT; standard-dose cytarabine with or without an anthracycline; intermediate-dose cytarabine alone (for patients who are more fit) or plus

daunorubicin and GO for patients with CD33-positive AML; intermediate-dose cytarabine and midostaurin for patients with *FLT3*-mutation–positive AML; or CPX-351 [cytarabine (65 mg/m$^2$) and daunorubicin (29 mg/m$^2$)], which is the preferred strategy if given during induction for patients with therapy-related AML, antecedent hematologic disorder, or AML-MRC. If the patient received more intensive regimens in induction and achieved a remission but had treatment-related toxicity that prevents the patient from receiving conventional consolidation or is not eligible for allogeneic HCT, maintenance therapy with HMAs may be appropriate.[251,320] In some cases, observation is recommended, as some patients have been able to maintain a CR without further treatment.

For patients who experience induction failure, a clinical trial, low-intensity therapy (azacitidine, decitabine), allogeneic HCT (preferably in the context of a clinical trial), therapies for R/R disease (see *Management of Relapsed/Refractory AML*), or best supportive care are recommended treatment options.

***Previous Lower-Intensity Therapy:*** For patients who previously received lower-intensity therapy, a marrow to document remission status upon hematologic recovery should be performed, with the timing dependent on the therapy used. If a response is observed, allogeneic HCT may be considered for select patients. Alternatively, low-dose therapies used in induction with demonstrated efficacy may be continued until progression, including venetoclax plus HMAs; venetoclax plus low-dose cytarabine; enasidenib (for *IDH2*-mutated AML); ivosidenib (for *IDH1*-mutated AML); glasdegib plus low-dose cytarabine; or HMAs alone or combined with sorafenib (for *FLT3*-mutant AML); or GO alone (a category 2B recommendation). If no response or progression is seen, a clinical trial, therapies for R/R AML (see *Management of Relapsed/Refractory AML*), or best supportive care are recommended treatment options.

**Principles of Venetoclax Use with HMAs or LDAC-Based Treatment**

With growing use of venetoclax-based therapies (ie, venetoclax with HMAs or low-dose cytarabine), and the fact that these therapies may be given for an indefinite duration as long as patients respond or derive hematologic benefit from the therapies, the AML Panel reviewed the literature and emerging guidelines that can inform a consensus on ways to optimize use of these therapies.[321]

For patients with newly-diagnosed disease, the panel notes that venetoclax with HMA or LDAC should be given concomitantly. The addition of a third targeted agent to these combinations is not recommended outside the context of a clinical trial. Prior to administering therapy, it is important to achieve a WBC count of <25,000/mcL with hydroxyurea, or leukapheresis if needed.[322] It is worth noting that the data supporting a beneficial role for leukapheresis in this context is limited.[323] In addition, venetoclax is a substrate of CYP3A4, so dose adjustments of venetoclax are recommended when concurrently using venetoclax with strong CYP3A4 inhibitors, most commonly the azole class of antifungal agents.[324] Reductions in duration of venetoclax and HMAs or LDAC may be considered in the setting of cytopenias. If during treatment, there is a need to discontinue any of the agents or a consideration to continue maintenance on single-agent venetoclax, the panel recommends referral to a tertiary cancer or academic medical center.

To minimize the development of tumor lysis syndrome—which is uncommon in this setting[322]—during the first cycle of treatment, inpatient treatment is strongly recommended especially through dose-escalation. The intrapatient dose escalation for venetoclax with HMA is 100 mg, 200 mg, and 400 mg given daily on days 1 to 3; and the intrapatient dose escalation for venetoclax with LDAC is 100 mg, 200 mg, 400 mg, and 600 mg given daily on days 1 to 4.[322] To minimize and avert further risk

of tumor lysis syndrome, the panel recommends aggressive monitoring of blood chemistries; monitoring and managing electrolyte imbalances; and treatment with allopurinol or other uric acid lowering agent.[322]

Venetoclax and HMAs have been shown to induce prolonged cytopenias even after achieving remission, and neutropenia is a dominant treatment-related toxicity associated with this combination of agents.[321] During the first cycle, the panel recommends continuing treatment regardless of cytopenias until a response assessment is made,[324] with aggressive transfusion support and supportive care as needed. The panel also recommends withholding growth factors until after the first cycle response assessment.[322] However, granulocyte colony-stimulating factors should be considered for patients who are neutropenic who have achieved morphologic remission but whose counts have not recovered. A bone marrow biopsy is necessary for response assessment on days 21–28 of the first cycle,[322] perhaps on the early end of this range for patients who receive the combination of venetoclax and decitabine.

If blasts are <5% during the first cycle, in the setting of cytopenias all treatment should be held and the following measures should be considered: growth factor support, if indicated; and a treatment-free interval for up to 14 days. When counts have recovered to a clinically significant threshold (ideally to CR or CRi), the next cycle of treatment can begin.[322] If counts have not recovered to a clinically significant threshold, consider repeating the BM biopsy. If morphological remission is ongoing, therapy can continue to be held or a second cycle can proceed with adjustments to dose or schedule of venetoclax and HMA or LDAC.[322]

During the second and subsequent cycles of treatment, if remission was observed after the first cycle, sequential cycles should continue with up to 14-day interruptions between cycles for count recover and/or growth factor support.[322] If there is no evidence of disease after the first cycle and assuming no unexpected changes in blood counts occur, the BM biopsy can be repeated at 3–6-month intervals, or as needed based on clinical suspicion for relapse, depending on the goals of the patient. If count recovery worsens over time, relapsed disease should be ruled out with a repeat BM biopsy.[322] If morphological remission is ongoing with worsening blood counts, consider decreasing the duration, and/or dose, of venetoclax and/or HMA or LDAC. However, if there is no morphological remission after the second cycle, consider enrollment in a clinical trial if available. If no clinical trial is available, and patient has experienced some response with manageable toxicity, therapy may be continued as long as it is tolerated.

If venetoclax and HMA or LDAC are being given to patients with relapsed/refractory (R/R) AML, the panel recommends antifungal prophylaxis.[321] Other recommendations for TLS, intrapatient dose escalation, BM biopsies, and cytopenia mitigation plans are similar to considerations that have been described.

**Role of MRD Monitoring**

MRD in AML refers to the presence of leukemic cells below the threshold of detection by conventional morphologic methods. Patients who have achieved a CR by morphologic assessment alone can still harbor a large number of leukemic cells in the bone marrow.[325] Due to the rapidly evolving nature of this field and the undeniable need for monitoring, MRD is still under investigation, with NCCN recommendations as discussed below.

While morphologic assessment is the first step in a cure for AML, there remains a level of MRD that currently lacks any standardized method of monitoring. Two of the most commonly used techniques are real-time quantitative PCR (RQ-PCR) and flow cytometry. RQ-PCR amplifies leukemia-associated genetic abnormalities, while flow cytometric profiling

detects leukemia-associated immunophenotypes (LAIPs).[326-328] Both methods have a higher sensitivity than conventional morphology. RQ-PCR has a detection range of 1 in 1000 to 1 in 100,000, while flow cytometry has sensitivity between $10^{-4}$ to $10^{-5}$. The challenge of incorporating these techniques into routine practice is a lack of standardization and established cutoff values, though ongoing research is focused on addressing these limitations. Most of what is known about MRD monitoring has been done in the APL population;[329,330] however, these techniques are now expanding to include other AML subtypes.[331] Emerging technologies include digital PCR and NGS.[325] NGS-based assays can be used to detect mutated genes through targeted sequencing gene panels,[332,333] though higher sensitivities are observed in PCR- and flow cytometry-based methods compared to conventional NGS.[325] The data from these methods have been correlated with AML treatment outcome and the preliminary results are promising. Refinement of these methods that take into account variables including the intrinsic nature of the transcript as well as factors of the patient population, including age, disease severity, and treatment, will make MRD monitoring in patients with AML a more reliable tool.

***RQ-PCR***

There are three classifications of RQ-PCR targets: leukemic fusion genes, mutations, and gene overexpression. The most investigated leukemic fusion genes are *RUNX1-RUNX1T1*, *CBFB-MYH11*, and *MLL* (*KMT2A*) fusion transcripts. Gene fusions are found in 20% and 35% of adult and childhood non-APL AML cases, respectively.[226,334] Mutations in AML include *NPM1*, *DNMT3A*, and *FLT3-ITD* mutations. *NPM1* mutations are seen in approximately one-third of adult AML cases, while less than 10% of childhood cases have this mutation.[335,336] Similarly, the *DMNT3A* mutation is found at a higher percentage in adult (15%–20%) compared to childhood (2%) AML.[75,337,338] The *FLT3-ITD* mutation is found in 25% of adult and 15% of childhood AML.[54,339] Two less well-studied mutations that may serve as MRD markers include *CEBPA* and *MLL*-partial tandem duplications.[340] Finally, the main target of gene overexpression in AML is the Wilms' tumor (*WT1*) gene. Taken together, these putative targets for MRD monitoring encompass the majority of AML cases.

A study of 29 patients with either *RUNX1-RUNX1T1* or *CBFB-MYH11* AML during postinduction and post-consolidation chemotherapy did not observe a correlation with survival.[341] However, the authors did correlate a greater than or equal to 1 log rise in RQ-PCR transcript relative to the remission bone marrow sample as indicative of inferior leukemia-free survival and imminent morphologic relapse.[341] Another study evaluated bone marrow from 53 patients during consolidation therapy and was the first to establish clinically relevant MRD cut-off values for the *CBFB-MYH11* transcript to stratify patients with increased risk of relapse.[242] PCR negativity in at least one bone marrow sample during consolidation therapy was predictive of a 2-year RFS of 79% as compared to the 54% seen in the setting of PCR-positivity. Similarly, Yin et al[244] found that a less than a 3-log reduction in *RUNX1-RUNX1T1* transcript in bone marrow or a greater than 10 *CBFB-MYH11* copy number in peripheral blood after 1 course of induction chemotherapy was highly predictive of relapse.[244] A study in 15 patients with childhood AML showed that increased *RUNX1-RUNX1T1* transcript levels were predictive of relapse.[342] *MLL* fusion transcripts for MRD monitoring have also been analyzed in 19 patients with t(9;11)(q22;q23) AML. Eleven of these patients showed negative PCR for the *MLL* fusion transcripts, which were associated with a better outcome. While most studies have shown a correlation between transcript level and outcome, a study of childhood AML showed RQ-PCR of *RUNX1-RUNX1T1* to be a poor marker for relapse and the method to be inferior to flow cytometry.[343] The different outcomes of the studies highlight the need for standardization of these methods. It also may be an indication of variability between adult and pediatric populations, a factor that must be considered when establishing methods and cutoffs.

The use of RQ-PCR in mutations is hampered by the inability to distinguish the number of cells containing transcripts, as each cell may have variable levels. Furthermore, these transcripts still may be detected in cells that have differentiated in response to treatment and are no longer clonogenic, thereby giving a false positive.[344,345] Another caveat is the instability of mutations that may result in false negatives. This is particularly true for *FLT3-ITD*[346-348] and *NPM1* mutations.[349-351] Despite these complications, several studies have correlated *NPM1* mutations and outcome.[112,350,352-357] In a small study of 25 patients, the use of a higher sensitivity RQ-PCR was shown to circumvent transcript instability, ultimately showing that *FLT3-ITD* MRD monitoring was predictive of relapse.[358] In comparison to *FLT3-ITD*, data suggest that *NPM1* mutations may be more stable.[352] Schittger et al[356] developed and tested primers for 17 different mutations of *NPM1*.[356] Serial analyses of 252 *NPM1*-mutated AML samples at 4 time points showed a strong correlation between the level of *NPM1*$^{mut}$ and outcome. Kronke et al[351] further modified this method to show that *NPM1*$^{mut}$ levels after double induction and consolidation therapy reflected OS and cumulative incidence of relapse.[351] In 245 patients, PCR negativity had a 6.5% 4-year cumulative incidence of relapse versus 53% for PCR positivity.[351] This correlation was also seen when taken after completion of therapy. In addition, an RQ-PCR analysis of 2596 samples from 346 patients with *NPM1*-mutated AML demonstrated that MRD was the only independent prognostic factor for mortality (HR, 4.84; 95% CI, 2.57–9.15; $P < .001$) and persisting *NPM1*-mutated transcripts were associated with relapse.[353]

*CEBPA* and *MLL*-partial tandem duplications are additional targets for MRD monitoring by RQ-PCR.[340,359] While data suggest both transcripts may be suitable MRD markers, the small sample sizes limit current use of these markers until data can be extrapolated to a larger population. Mutations associated with clonal hematopoiesis of indeterminate potential (CHIP) and aging including *DNMT3A*, *TET2*, and potentially *ASXL1*, are not considered reliable MRD markers.[332,333,360]

Gene overexpression studies have focused on WT1. Retrospective data show that a lower level of WT1 after induction therapy is associated with long-term remission.[361] A meta-analysis of 11 trials, encompassing 1297 patients, showed the poor prognostic significance of WT1 level.[362] WT1 was overexpressed in 86% of marrow and 91% of blood samples from 504 patients with AML when compared to 204 healthy donors.[363] However, when using the cutoff values of greater than 100-fold detection, only 46% of blood and 13% of marrow samples in the cohort were positive.[363] This reflects the outliers of the healthy population that have higher WT1 transcripts. Furthermore, only 19% of childhood AML samples met this criterion in a study.[364] While WT1 is a strong candidate for MRD monitoring, early studies show that there is variability in the detection of this transcript that must first be addressed. In a retrospective study of patients with AML who underwent allogeneic HCT (n = 74), a multigene MRD RQ-PCR array predicted clinical relapses occurring in the first 100 days after allogeneic HCT compared with 57% sensitivity using WTI RQ-PCR alone.[365] Notably, for patients who achieved CR prior to allogeneic HCT, the presence of pre-transplantation MRD positivity in peripheral blood testing was associated with survival similar to patients with pathologist bone marrow-based diagnosis of active disease.[365]

***Flow Cytometry***

Flow cytometry for the monitoring of AML measures the presence of tumor-specific antigens and abnormalities not found on normal bone marrow cells. Several known markers identify abnormal cells or cell maturation, and when used as a panel these markers can define cell populations.[366] Studies in both adult and childhood AML cases show a correlation between flow cytometry and relapse. Loken et al[367] showed that 7 of 27 patients who had not achieved morphologic remission had

negative MRD by flow cytometry. All 7 patients were long-term survivors when compared with the remaining 20 patients. Conversely, in a separate study of 188 patients who achieved morphologic remission, less than 5% had high levels of MRD by flow cytometry.[367] A larger study of 1382 follow-up bone marrow samples from 202 children with AML demonstrated MRD to be a predictor of relapse. In this study 28 of the 38 samples (74%) with greater than 15% myeloblasts had measurements of 0.1% or greater by flow cytometry. In patients with 5% to 15% myeloblasts, 43 of the 129 patients (33%) were detected by the same threshold and only 100 of the 1215 samples (8%) with less than 5% myeloblasts fell into this category. The ability of MRD monitoring to predict an unfavorable EFS was statistically significant ($P < .0001$).[343] In a study of adult patients with AML who underwent allogeneic HCT from peripheral blood or bone marrow donor (n = 359), pre-transplant staging with flow cytometry demonstrated similar outcomes in 3-year OS and PFS estimates between patients experiencing MRD-positive morphologic remission and patients with active disease (26% vs. 23% and 12% vs. 13%, respectively) when compared to patients who achieved MRD-negative remission (73% and 67%, respectively).[368]

The most difficult issue facing flow cytometry as an effective method for MRD monitoring is standardization and training. Flow cytometry relies heavily on the expertise of the technician who must take into account variability in instruments, fluorochromes, analysis software, and individual antigens. Variations in the treatment schedule, dosing, type of treatment, and time of draw are also potential variables. Despite the issues with flow cytometry, research is focused on improving the method by defining threshold cutoff values[369-372] as well as generating standards to equalize data among different instruments and software programs. A study by Feller et al[373] further defined LAIPs and evaluated whether data from an established MRD monitoring laboratory could be replicated in four centers with no significant prior experience. Increased success rates of defining LAIPs were seen in all four centers after extensive group discussion. The inexperienced laboratories had a success rate of 82% to 93% for defining at least one LAIP in a sample from 35 evaluable samples. The missed LAIPs would have resulted in 7% to 18% of the patients being unevaluable by MRD in these centers. The number of samples incorrectly evaluated increases if they included samples in which at least two LAIPs were identified by the primary lab, but the other labs only detected one LAIP. This accounted for an additional 9% to 20% of cases that would have resulted in false negatives. LAIPs with high specificity and sensitivity (MRD levels of .01%) were very well-defined in the multicenter analysis. With regard to the missed LAIPs, the authors proposed the design of redundant panels to account for immunophenotypic shift. Inconsistencies in LAIPs with MRD of 0.1% or lower may be resolved with the use of a greater number of fluorochromes.[374] Another important conclusion from this publication was the ability of these methods to be applied to different instruments; both the Beckman Coulter and the Becton Dickinson instruments were tested and obtained similar results. MRD monitoring is a more feasible option if performed in core facilities until greater research is done on the method to eliminate variability. Enrollment in clinical trials that provide MRD monitoring is encouraged.

Because a high-quality sample is essential for reliable treatment evaluation, the NCCN AML Panel recommends that the optimal sample for MRD assessment is either peripheral blood for *NPM1* PCR-based techniques or the first pull/early pull of the bone marrow aspirate for other PCR-, flow cytometry- and NGS-based assays. The timing of MRD assessments will vary and depend on the regimen used,[243,353] but may occur after completion of initial induction[332,333,360] and before allogeneic transplantation.[375]

### Postremission Surveillance for AML

Monitoring for CBCs, including platelets, every 1 to 3 months for the first 2 years after patients have completed consolidation therapy, then every 3 to 6 months thereafter up to 5 years, is recommended. Bone marrow evaluation should be performed only if the hemogram becomes abnormal, rather than as routine surveillance at fixed intervals, unless the bone marrow evaluation is being performed as part of a clinical research protocol.

If no sibling donor has been identified, a donor search should be initiated at first relapse in appropriate patients concomitant with initiation of reinduction therapy. At relapse, the panel suggests conducting comprehensive molecular profiling using appropriate material to determine the mutation status of actionable genes including *FLT3* (ITD and TKD), *IDH1*, and *IDH2* because it may guide selection of appropriate therapies (see *Management of Relapsed/Refractory AML*) and enrollment in appropriate clinical trials. Ongoing studies are evaluating the role of molecular monitoring in the surveillance for early relapse in patients with AML (see *Role of MRD Monitoring*).

### Management of Relapsed/Refractory AML

Treatment of R/R AML is challenging and outcomes are poor.[21,376] Many studies have also demonstrated that lack of early blast clearance or lack of response to the first induction cycle are major predictors for poor outcomes.[21,377,378] Intensive regimens generally achieve high second CR rates but do not generate substantial CR duration.[379] Currently, allogeneic HCT at second CR is associated with relatively lower rates of relapse and represents the only potentially curative option.[21,376,380] Emerging data are demonstrating the utility of targeted therapies in R/R AML.[381]

#### *Targeted Therapy*

***FLT3-Positive AML***: In a phase I/II study, the safety and tolerability of gilteritinib, a *FLT3* inhibitor, was assessed in adult patients with R/R AML (n = 252).[306] In this group, 58 patients had wild-type *FLT3* AML and 194 patients had *FLT3*-mutated AML (*FLT3*-ITD, n = 162; *FLT3*-TKD/*FLT3* D385, n = 16), and received oral gilteritinib (20–450 mg) once daily in one of seven dose-escalation or dose-expansion cohorts.[306] Gilteritinib was well-tolerated in this patient subpopulation and the most common grade 3 or 4 adverse events were febrile neutropenia (39%), anemia (24%), thrombocytopenia (13%), sepsis (11%) and pneumonia (11%).[306] The ORR in all patients with R/R AML was 40%, which was improved to 52% in patients with *FLT3*-mutated AML treated with gilteritinib doses ≥80 mg/day.[306]

In a phase 3 trial, the efficacy of gilteritinib was compared to conventional chemotherapy used to treat R/R AML (n = 371).[307] In this study, the four chemotherapy options included two high-intensity options (FLAG-Ida; and mitoxantrone plus etoposide and cytarabine [MEC]) and two low-intensity options (low-dose cytarabine and azacitidine). Of the 371 eligible patients, 247 were randomly assigned to the gilteritinib group (120 mg/day) or the salvage chemotherapy group (n = 124). The percentage of patients who had CR with full or partial hematologic recovery was 34% and 15.3% in the gilteritinib and chemotherapy groups, respectively.[307] The median OS was significantly longer in the gilteritinib group compared to the chemotherapy group (9.3 months vs. 5.6 months; HR, 0.64; 95% CI, 0.49–0.83; $P < .001$).[307] In addition, the median EFS was longer in the gilteritinib group when compared to the chemotherapy group at 2.8 months versus 0.7 months, respectively (HR for treatment failure or death, 0.79; 95% CI, 0.58–1.09).[307] Based on

these data, gilteritinib was approved by the FDA in November 2018 for the treatment of adult patients who have R/R AML with a *FLT3* mutation.

In a phase II study, the efficacy of azacitidine and sorafenib, a *FLT3* inhibitor, was evaluated in adult patients with R/R AML (n = 43; median age, 67 years; range, 24–87 months).[382] The response rate was 46%, with CR, CR/CRi, and PR rates of 16%, 27%, and 3%, respectively.[382] In addition, the degree of *FLT3*-ITD inhibition appeared to correlate with plasma sorafenib concentrations.

***IDH Mutation-Positive AML*:** The studies evaluating the efficacy of ivosidenib[301] and enasidenib[300] in *IDH1*- and *IDH2*-mutation positive R/R AML, respectively, have been summarized in a previous section under *Management of AML in Patients >60 Years*, for patients who are not candidates for or decline intensive remission induction therapy.

***CD33-Positive AML***: In a study by Taksin et al, adult patients with AML in first relapse (n = 57) received fractionated doses of GO, given at a dose of 3 mg/m$^2$ on days 1, 4, and 7 for one course.[383] Fifteen patients achieved CR (26%) and 4 achieved CRp (7%). The median RFS was similar for patients who achieved CR and CRp and was 11 months.[383] In addition, no veno-occlusive disease (sinusoidal obstructive syndromes) occurred after GO treatment or after GO followed by HCT (n = 7), although the authors recommended a minimum delay of 90 days between GO treatment and HCT.[383]

***Chemotherapy***

The guidelines provide a list of several commonly used regimens for R/R disease that are grouped as either aggressive or less aggressive therapy (see *AML: Therapy for Relapsed/Refractory Disease* in the algorithm). The regimens grouped under aggressive therapy represent purine analog (eg, fludarabine, cladribine, clofarabine)–containing regimens, which have shown remission rates of approximately 30% to 45% in several clinical trials, and those that have been used as the comparator arms in U.S. cooperative group trials in the past decade.

A study by Robak et al evaluated the efficacy of cladribine, cytarabine, and G-CSF as re-induction therapy in patients with R/R AML (n = 20).[384] Ten patients (50%) achieved CR with a median duration of 22.5 weeks (range, 3.5–53 weeks). Two patients experienced PR (10%) and 8 patients did not have response to therapy.[384] In another study, the efficacy of cladribine, cytarabine, and idarubicin was analyzed in patients with R/R AML (n = 34).[385] After at least one cycle of treatment, 18 patients (52.9%) achieved CR and 16 (47.1) received subsequent allogeneic HCT.[385]

In a study of patients with resistant or relapsing AML (n = 38), patients were treated with fludarabine, cytarabine, and G-CSF, and overall 21 patients (55%) achieved CR.[386] In a study by Parker et al, patients with high-risk MDS/AML (n = 19; including R/R AML, n = 7), treated with fludarabine, cytarabine, G-CSF, and idarubicin experienced response to therapy, with 12 patients (63%) achieving CR.[387]

In a phase I study, a regimen with clofarabine, cytarabine, and idarubicin was evaluated in a subgroup of adult patients with R/R AML (n = 21) and 10 patients (48%) achieved CR.[388] A regimen with clofarabine (40 mg/m$^2$) combined with cytarabine (2 g/m$^2$) was evaluated in a randomized, placebo-controlled, phase III trial (CLASSIC I trial) in R/R AML, resulting in an ORR of 47% (CR rate, 35%) and a median OS of 6.6 months.[389] A retrospective study compared clofarabine versus fludarabine in combination with HiDAC with or without G-CSF.[390] Patients treated with a clofarabine-based regimen (n = 50) compared to a fludarabine-based regimen (n = 101) had a higher CR rate (OR, 9.57; $P < .0001$) and a longer survival (mortality HR, 0.43; $P = .0002$).[390]

The regimens for R/R AML grouped under less aggressive or less intensive therapy include HMAs (azacitidine or decitabine), low-dose

cytarabine, and venetoclax-containing regimens. Emerging studies suggest that venetoclax in combination with HMAs or low-dose cytarabine has demonstrated antileukemic activity in R/R AML, MDS, and BPDCN.[391] A study suggests that azacitidine followed by donor lymphocyte infusions (DLIs) may be a treatment option for therapy in patients who have AML that relapses after allogeneic HCT.[392] These data are based on a prospective phase II trial of 28 patients with AML. In this study, 22 patients received DLIs and an ORR of 30% was achieved. This included 7 CRs and 2 PRs. At publication, 5 patients remained in CR with a median of 777 days (range, 461–888 days). Neutropenia and thrombocytopenia grade III/IV were the most common adverse events (65% and 63%, respectively). Acute and chronic graft-versus-host disease (GVHD) were seen in 37% and 17% of patients, respectively. Correlations suggest a better response in patients with myelodysplasia-related changes ($P$ = .011) and lower blast count ($P$ = .039) or patients with high-risk cytogenetics ($P$ = .035). However, interpretation of results is limited by the small size of the study.[392]

***NCCN Recommendations***

The NCCN AML Panel recommends enrollment in a clinical trial for the management of R/R AML as a strongly preferred option. Other options include targeted therapy or chemotherapy followed by allogeneic HCT. For targeted therapies, the guidelines provide a list of options including gilteritinib for patients with *FLT3* mutations (a category 1 recommendation). Sorafenib may be added to HMAs (azacitidine or decitabine) for patients with *FLT3*-ITD mutations. Other targeted therapy options include GO for patients with CD33-positive AML, and ivosidenib or enasidenib for patients with *IDH1* or *IDH2* mutations, respectively.

The regimens for aggressive therapy include: 1) cladribine, cytarabine, and G-CSF, with or without mitoxantrone or idarubicin;[384,385] 2) HiDAC, if not previously received in treatment, with or without anthracycline[240]; 3) fludarabine, cytarabine, and G-CSF (FLAG regimen) with or without idarubicin;[386,387] 4) etoposide and cytarabine, with or without mitoxantrone[393,394]; 5) clofarabine and cytarabine with or without idarubicin;[388,389] or 6) clofarabine with or without idarubicin.[395,396] Less aggressive or less intensive treatment options may include: 1) HMAs alone (azacitidine or decitabine)[282,289,397]; 2) low-dose cytarabine[294,398] (a category 2B recommendation); or 3) venetoclax combined with HMAs or low-dose cytarabine.[309,391] Best supportive care is always an option for patients who cannot tolerate or do not wish to pursue further intensive treatment.

In some cases, if a patient has experienced a long first remission (≥12 months), repeating treatment with a successful induction regimen may be considered. This strategy primarily applies to cytotoxic chemotherapy regimens and excludes the use of dual-drug encapsulation of cytarabine and daunorubicin, and the re-use of targeted agents due to the potential development of resistance. Targeted therapies may be retried if they were not administered continuously and not stopped due to the development of clinical resistance. If a second CR is achieved, consolidation with allogeneic HCT should be considered.



## Supportive Care for Patients with AML

Although variations exist between institutional standards and practices, several supportive care issues are important to consider in the care of patients with AML. In general, supportive care measures may include the use of blood products for transfusion support and correction of coagulopathies, tumor lysis prophylaxis, anti-infective prophylaxis, and growth factor support. Monitoring for neurologic and cardiovascular toxicities may be required for particular therapeutic agents (HiDAC or ATO) or because of patient-specific comorbidities. These supportive care measures are tailored to address the specific needs and infection susceptibility of each individual.

When transfusion support is required, leukocyte-depleted blood products should be used for transfusion. All patients with AML are at risk for acute GVHD and management should be based on institutional practice or preference. Cytomegalovirus (CMV) screening for potential HCT candidates is left to institutional policies regarding provision of CMV-negative blood products to patients who are CMV-negative at the time of diagnosis. HLA typing is routinely used in many institutions to select platelet donors for patients who exhibit alloimmunization to HLA-specific antigens.

Standard tumor lysis prophylaxis includes hydration with diuresis, and allopurinol administration or rasburicase treatment. Rasburicase is a genetically engineered recombinant form of urate oxidase enzyme. Rasburicase should be considered as initial treatment in patients with rapidly increasing blast counts, high uric acid, or evidence of impaired renal function.[399] When possible, patients should be evaluated for glucose-6-phosphate dehydrogenase (G6PD) deficiency, as rasburicase use in these patients is contraindicated and is associated with an increased risk of inducing hemolysis.[400,401] Urine alkalinization was previously recommended as a means to increase uric acid solubility and reduce the potential for uric acid precipitation in the tubules. However, this method is not generally favored as there are no data to support this practice and similar effects could be seen with saline hydration alone.[402] Alkalinization can complicate care by increasing calcium phosphate deposits in vital organs (eg, kidney, heart) as a result of hyperphosphatemia. Furthermore, in contrast to allopurinol, rasburicase has the added benefit of rapid breakdown of serum uric acid, eliminating the need for urine alkalinization.

Patients who receive HiDAC should be closely monitored for changes in renal function, because renal dysfunction is highly correlated with increased risk of cerebellar toxicity. Patients should be monitored and assessed for nystagmus, dysmetria, slurred speech, and ataxia before each dose of HiDAC; patients exhibiting any neurologic signs should discontinue HiDAC, and all subsequent cytarabine therapy must be administered as standard dose. Patients who develop cerebellar toxicity should not be rechallenged with HiDAC in future treatment cycles.[403] HiDAC should also be discontinued in patients with rapidly rising creatinine caused by tumor lysis.

Decisions regarding the use and choice of antibiotics to prevent and treat infections should be made by the individual institutions based on the prevailing organisms and their drug resistance patterns.[404] Greater detail regarding the prevention and treatment of cancer-related infections can be found in the NCCN supportive care guidelines (see NCCN Clinical Practice Guidelines for Prevention and Treatment of Cancer-Related Infections) and commensurate with the institutional practice for antibiotic stewardship.

Growth factors (G-CSF or granulocyte macrophage colony-stimulating factor [GM-CSF]) are not recommended during induction for patients with APL as they can complicate assessment of response and increase the risk of differentiation syndrome. However, in patients with AML (non-APL), growth factors may be considered during induction for patients who are septic and who have a life-threatening infection in an attempt to shorten the duration of neutropenia. Some regimens such as FLAG incorporate G-CSF into the regimen. However, the use of growth factors may complicate the interpretation of marrow results. There is a recommendation to discontinue colony-stimulating factors at least a week before a planned marrow sample to assess remission status.

There is no evidence for whether growth factors have a positive or negative impact on long-term outcome if used during consolidation. Growth factors may be considered as part of supportive care for postremission therapy. Growth factors are not routinely recommended in postremission therapy, except in life-threatening infections or when signs

and symptoms of sepsis are present and the leukemia is believed to be in remission.

### Supportive Care for Patients with AML Who Prefer Not to Receive Blood Transfusions

There is no established treatment of AML that does not require use of blood and blood products for supportive care, and with limited data, providing guidelines or recommendations for AML management in this context is challenging. However, the AML panel recognizes that this is a significant issue faced in a narrow spectrum of clinical settings. In this context, the panel reviewed the existing literature and collective experience with this issue and summarized some considerations to guide treatment and supportive care. However, it is important to note that the panel believes that in many cases, good outcomes from these strategies are rare.

At the outset, it is important to discuss the goals of care with the patient and establish an understanding of the complications that can arise without transfusions. In addition, it will be helpful to ascertain if the patient will accept certain blood products (eg, cryoprecipitate) and stem cells (either autologous or from another donor source). To mobilize peripheral blood stem cells and/or bring up hemoglobin levels prior to peripheral blood stem cell transplantation, some treatment centers have used erythropoietin stimulating agents (ESAs), G-CSF, and thrombopoietin (TPO) mimetics.[405-407] However, before using this strategy, the potential risks, benefits and uncertainties of using these agents in this context should be thoroughly discussed. Consider referring the patient to centers with expertise in bloodless autologous transplant.[406,407] In addition, for patients who are Jehovah's Witnesses and for this reason decline blood transfusions, the U.S. branch of the Christian Congregation of Jehovah's Witness has Hospital Liaison Committees that may provide helpful information about bloodless medicine.

Regarding treatment options, the panel recommends considering less myelosuppressive induction including dose reduction of anthracyclines and use of non-intensive chemotherapy.[408-412] Some of these options may include targeted agents guided by testing for actionable mutations instead of intensive chemotherapy, especially in a noncurative setting. However, the panel notes that dose reductions in chemotherapy without transfusion support in patients with AML is associated with a lower rate of remission, high mortality by severe anemia, and is unlikely to result in durable remissions.[411] During treatment, measures should be taken to minimize blood loss and decreased the risk of bleeding including: the use of pediatric collection tubes; avoiding concomitant medications or procedures that increase the risk of bleeding or myelosuppression; use of oral contraceptive pills or medroxyprogesterone acetate in menstruating individuals; or proton pump inhibitors, as indicated.[406,413] Vitamin K may be considered as an adjuvant to improve coagulopathy.[406,413] In patients at risk of bleeding (eg, when platelet counts drop below 30,000/mcL), aminocaproic acid or tranexamic acid may be considered to manage bleeding.[406,413] In patients with elemental or vitamin deficiencies, consider iron, folate, and vitamin B12 supplementation.[406,413] In patients with severe anemia, consider bed rest and supplemental oxygenation.[406,413]

### Evaluation and Treatment of CNS Leukemia

Leptomeningeal involvement is much less frequent (<3%) in patients with AML than in those with ALL; therefore, the panel does not recommend LP as part of the routine diagnostic workup. However, if neurologic symptoms (eg, headache, confusion, altered sensory input) are present at diagnosis, an initial CT/MRI should be performed to rule out the possibility of intracranial hemorrhage or presence of a mass or lesion. If no mass effect is seen, cerebrospinal fluid cytology should be sampled by LP. If the LP is

negative for leukemic cells, the patient can be followed with a repeat LP if symptoms persist. If the LP is positive by morphology or immunotype by flow cytometry, IT chemotherapy is recommended, given concurrently with systemic induction therapy. If LP result is equivocal, consider repeating LP with morphology or immunotype by flow cytometry to delineate involvement. IT therapy may include agents such as IT methotrexate or IT cytarabine either alone or combined. The selection of agents and dose schedules for IT therapy largely depend on the specific clinical situation (eg, extent of CNS leukemia, symptoms, systemic therapies given concurrently) and institutional practices. Initially, IT therapy is generally given twice weekly until the cytology shows no blasts, and then weekly for 4 to 6 weeks. Importantly, IT therapy should only be administered by clinicians with experience and expertise in the delivery of IT agents. HiDAC has significant penetration across the blood–brain barrier and may represent an alternative to repeated IT injections during induction therapy. The cerebrospinal fluid must then be reassessed after completion of induction therapy, and further IT therapy should be given as appropriate.

If the initial CT/MRI identifies a mass effect or increased intracranial pressure due to a parenchymal lesion in the brain, a needle aspiration or biopsy may be considered. If the results are positive, then radiation therapy is recommended, followed by IT therapy, as described earlier. IT therapy or HiDAC should not be administered concurrently with cranial radiation because of the increased risks of neurotoxicity. Another option for these patients includes HiDAC-containing therapy with dexamethasone to help reduce intracranial pressure.

The panel does not recommend routine screening for occult CNS disease in most patients with AML in remission. The exceptions are patients with extramedullary disease, monocytic differentiation, biphenotypic leukemia, WBC count greater than 40,000/mcL at diagnosis, high-risk APL, or *FLT3* mutations. For patients with positive cerebrospinal fluid by morphology or immunotype by flow cytometry, the panel recommends either IT chemotherapy, as outlined earlier, or documenting clearance of CNS disease after the first cycle of HiDAC chemotherapy. In addition to the recommended evaluation and treatment of CNS leukemia, further CNS surveillance should be followed based on institutional practice

## Management of Blastic Plasmacytoid Dendritic Cell Neoplasm

BPDCN is a rare myeloid malignancy, representing only 0.44% of hematologic malignancies, with an incidence of 0.04 cases per 100,000 people in the United States.[414,415] BPDCN, which was formerly known as blastic natural killer cell lymphoma or granular $CD4^+/CD56^+$ hematodermic neoplasm, was renamed in the 2008 WHO classification with the evolving knowledge of its plasmacytoid dendritic cell (PDC) origin.[416,417] In 2016, it was recognized as a unique myeloid malignancy.[67] Pathologically, it is characterized by aggressive proliferation of precursors of PDCs.[418,419] The etiology of BPDCN is unknown, but its association with MDS or CMML in some cases may suggest a related pathogenesis.[418,420] BPDCN is associated with a poor prognosis, with median OS of approximately 8-12 months when patients are treated with chemotherapy.[419,421] Median age of presentation is 65 to 67 years, with an approximate male-to-female ratio of 3:1. The most frequent clinical presentation of typical BPDCN cases is asymptomatic solitary or multiple skin lesions that can disseminate rapidly without therapy.[418,419] Peripheral blood and bone marrow involvement may be minimal at presentation, but tend to develop as the disease progresses. Additional sites of involvement can include lymph nodes, spleen, and other extramedullary organs.[417,418,422] Less commonly, patients may present with features of an acute leukemia without skin manifestations.[419] CNS involvement is not infrequent; approximately 10% of patients who present with neurological symptoms at diagnosis have confirmed CNS involvement[423] and rates of CNS involvement, both at diagnosis and at relapse, have been found to be in the range of 9-26% in several additional studies.[419,424,425]

### Workup

The evaluation and initial workup for suspected BPDCN consists of a comprehensive medical history and physical examination. Laboratory evaluations include a comprehensive metabolic panel and a CBC including platelets and a differential of WBCs. Analyses of peripheral blasts, bone marrow biopsy and aspirate, biopsy of skin lesions and, if suspected to be involved, lymph nodes and other tissues are recommended. These analyses should include dendritic cell morphology assessment, immunohistochemistry, flow cytometry, cytogenetic analysis (including karyotyping and/or FISH), and molecular analyses. Analysis of skin lesions often occurs in collaboration with dermatology. It is essential to differentiate the skin lesions of BPDCN from other neoplastic and non-neoplastic skin lesions and rashes, including leukemia cutis associated with AML, and analysis by experienced hematopathologists is often required.[417] If extramedullary disease and/or lymphadenopathy is suspected, a PET/CT scan is recommended. A lumbar puncture is highly recommended at initial diagnosis to rule out CNS disease, and subsequent IT prophylaxis is strongly encouraged even in the absence of known CNS disease.[417]

The diagnosis of BPDCN can be difficult due to overlapping morphological, immunophenotypic, and clinical features of other hematologic malignancies, such as AML.[417] This is particularly true when BPDCN presents as isolated cutaneous lesions, as biopsy specimens from cutaneous lesions may not yield sufficient cells for appropriate flow cytometric analysis.[417] A diagnosis of BPDCN requires expression of at least 4 of these 6 antigens on malignant cells: CD123 (also referred to as interleukin-3 receptor-alpha [IL3Rα]), CD4, CD56, TCL-1, CD2AP, and CD303/BDCA-2, in the absence of lineage-specific markers.[417,418] TCF4/CD123 coexpression has also been found to be a sensitive and specific diagnostic marker for BPDCN.[426,427] CD303 is emerging as

another marker useful in the diagnosis of BPDCN and may serve as a potential marker for further directed therapy.[428] BPDCN must be distinguished from mature plasmacytoid dendritic cell proliferation (MPDCP) in which PDCs are morphologically mature and CD56-negative.[418] In addition, recurrent mutations in the following genes have been described: ASXL1, IDH1, IDH2, IKZF1, IKZF2, IKZF3, NPM1, NRAS, TET1, TET2, TP53, U2AF1, and ZEB2.[417,418,429,430]

### Induction Therapy for Patients with BPDCN

Given the rarity of BPDCN, no standardized chemotherapy approach has been established.[419] Historically, therapeutic approaches have varied widely and have included irradiation for localized skin lesions, lymphoma- or leukemia-type chemotherapy regimens, and HCT.[431] Despite good initial responses to chemotherapy, with response rates of 40-90%[417], early relapse rates are high, even among those who achieve CR.[417,419,431] CD123-targeted therapy with tagraxofusp-ersz has more recently emerged as the preferred treatment option in appropriate candidates.

Recently, a collaborative initiative, the North American BPDCN Consortium (NABC), made up of a group of experts from multiple areas of expertise, has been formed to define the current standard of care for management of BPDCN and to identify future areas of research.[432]

#### *CD123-Targeted Therapy*

CD123, or IL3Rα, overexpression is present in virtually all cases of BPDCN.[422] Tagraxofusp (formerly SL-401) is a recombinant fusion protein made up of the catalytic and translocation domains of diphtheria toxin fused to IL3 that has shown activity against BPDCN.

The first prospective study of treatment of patients with BPDCN included 11 patients with recurrent or refractory BPDCN or who were not candidates for chemotherapy were treated with SL-401.[433] Each cycle of SL-401 treatment was comprised of a 12.5µg/kg dose administered over a 15-minute infusion every day for up to 5 doses. Of 9 evaluable patients who received treatment, 5 had a CR and 2 had a PR after one cycle of SL-401 treatment (78% ORR). The median duration of response was 5 months (range, 1–20+ months), with responses occurring in all sites of disease, including skin, bone marrow, and lymph nodes. Acute infusion-related adverse events such as fever, chills, and nausea were mild to moderate in severity and were most commonly seen within the first several hours after SL-401 infusion; however, these symptoms were occasionally noted up to 4-8 hours following infusion. Premedications including acetaminophen, diphenhydramine, methylprednisolone, and famotidine were given, likely mitigating these events. Resulting symptoms following infusion responded to additional dosing of acetaminophen, meperidine, antiemetics, and/or H1- and H2-histamine antagonists. These acute infusion-related events may be related to cytokine release from necrotic cells and damaged BPDCN blasts. Most patients experienced one or more symptoms suggestive of vascular or capillary leak syndrome, such as hypoalbuminemia, edema, hypotension, and hyponatremia. Hypoalbuminemia was the most consistent and early manifestation of capillary leak syndrome (grade 1 in 4 patients, grade 2 in 6 patients). Symptoms of capillary leak syndrome were managed by the administration of parenteral albumin and diuretics. Though several patients experienced grade 3 thrombocytopenia and neutropenia, myelosuppression was generally modest and reversible, potentially reflecting the minimal expression of IL3R on normal myeloid progenitors. Many patients experienced transaminitis without hyperbilirubinemia, with onset typically 5-10 days post-infusion and with full resolution typically 15-21 days following infusion.

In a multicohort study by Pemmaraju and colleagues, 84 patients with untreated or relapsed BPDCN were treated with an IV infusion of tagraxofusp at a dose of 12 µg/kg on days 1 to 5 of each 21-day cycle.[434] Treatment was given until disease progression or unacceptable adverse

effects. Of the 84 patients, 65 received first-line treatment and 19 had received prior treatment. Among evaluable patients who received first-line treatment of tagraxofusp, the primary outcome (CR and clinical CR) was observed in 57% of patients, ORR was 75%, and median OS was 15.8 months. Of the patients who achieved CR or clinical CR following first-line treatment of tagraxofusp, 51% were successfully bridged to HCT (allogeneic HCT, n = 13; autologous HCT, n = 6) while in remission and median OS in this subgroup was 38.4 months. Of the 18 patients who achieved CR or clinical CR following first-line treatment who did not proceed to HCT, 4 had duration of responses >6 months. Among the 19 patients who had received prior therapy, ORR was 58% with a median OS of 8.2 months. Among this subgroup, 1 patient was successfully bridged to HCT. Based on earlier data from this trial[422], the FDA approved tagraxofusp-erzs for the treatment of BPDCN in adults and pediatric patients ≥2 years of age in 2018.

The most common adverse events noted in the Pemmaraju study were increased levels of alanine aminotransferase (ALT) and aspartate aminotransferase (AST), hypoalbuminemia, fatigue, fever, thrombocytopenia, nausea, and peripheral edema.[434] In addition, capillary leak syndrome was observed in 21% of patients (8 of which were grade ≥3 and 3 of which were grade 5 resulting in death), primarily in the first cycle of treatment. Median time to onset of capillary leak syndrome was 6 days (range 3-51 days), with a median duration of 6 days (range 3-69 days). Capillary leak syndrome was managed by withholding further doses of tagraxofusp, administering IV albumin or glucocorticoids, and careful management of volume status.

***Chemotherapy***

In a retrospective multicenter study, 41 patients with BPDCN received induction treatment with AML-type regimens (n = 26) and ALL-type/lymphoma-type regimens (n = 15).[419] The AML-type treatment protocols included MEC (mitoxantrone, cytarabine, etoposide), ICE (idarubicin, cytarabine, etoposide), standard-dose cytarabine and anthracycline (7+3), FLAG, and FLAG-Ida. The ALL/lymphoma-type regimens included hyper-CVAD (alternative cycles of hyperfractionated cyclophosphamide, vincristine, doxorubicin, dexamethasone, methotrexate, and cytarabine), GIMEMA ALL trial therapy (association of doxorubicin, vincristine, prednisone, and asparaginase), CHOP (cyclophosphamide, doxorubicin, vincristine, and prednisone), and CHOEP (CHOP plus etoposide). There were patients who required additional therapy based on extramedullary disease (4 patients received IT chemotherapy for CNS involvement and 2 patients received radiation therapy for skin lesions). 14% of patients underwent allogeneic HCT at some point in their course of therapy. After induction, the overall CR rate was 41%, with 7 patients achieving CR after AML-type induction, and 10 patients achieving CR after ALL-type induction. The median OS was 8.7 months (range, 0.2–32.9), and patients who received ALL-type chemotherapy appeared to have longer OS compared to patients treated with AML-type chemotherapy (12.3 vs. 7.1 months, respectively; $P = .02$). In addition, the median OS of patients who received transplant was significantly higher than non-transplanted patients (22.7 vs. 7.1 months, respectively; $P = .03$). Age was also noted to be a significant prognostic factor, with a median OS of 12.6 months in patients <65 years compared to 7.1 months for those >65 years ($P = .04$). Relapses occurred in 35% of patients at a median of 9.1 months.

An additional retrospective study analyzed the impact of 4 different chemotherapeutic approaches: 1) local therapy or systemic regimens less aggressive than CHOP, 2) CHOP and CHOP-like regimens, 3) acute leukemia regimens, and 4) allogeneic or autologous HCT.[431] Therapies less intensive than CHOP were a heterogenous group, including local radiation, systemic steroids, and supportive care, but were mostly cyclophosphamide-based chemotherapy regimens. Though this group had

a high ORR of 80% (68% CR), only 7% of patients had a sustained CR and the median OS for evaluable patients was 9 months. Patients in the CHOP and CHOP-like regimens arm had similar results despite therapy being more aggressive, with an ORR of 70% (55% CR) and only 1 case of sustained CR. Intensive acute leukemia regimens resulted in a CR rate of 94%, with approximately 1/3 of patients experiencing a sustained CR. There were 10 evaluable patients in the HCT arm (6 allogeneic, 4 autologous). Median OS was 38.5 months in the allogeneic arm compared to 16.5 months in the autologous arm. At the time of publication, all but one patient who had undergone allogeneic HCT in first remission remained disease-free.

Another retrospective study evaluated the diagnostic flow cytometry pattern and outcome of nine patients with BPDCN after front-line treatment with hyper-CVAD.[435] In this group, seven patients received induction treatment with hyper-CVAD and had a CR of 67% and ORR of 86%. Five of the six patients who responded to therapy received planned allogeneic HCT. With a median follow-up of 13.3 months, the one-year DFS and OS rates for all patients were 56% and 67%, respectively. The 1-year DFS for those who received allogeneic HCT was 80%. The 1-year OS for patients who received allogeneic HCT was 80%, compared to 50% in those who received chemotherapy alone. The median OS was 7.9 months for those who received chemotherapy alone.

A more recent retrospective study compared outcomes of 100 patients with BPDCN treated with frontline hyper-CVAD-based therapy (n= 35), tagraxofusp (n = 37) or other therapies (n = 28.[436] The highest CR rates were seen with hyper-CVAD based therapy (80%), followed by tagraxofusp (59%), and finally other regimens (43%) (*P* = .01), though there was no significant difference in OS (28.3 vs 13.7 vs 22.8 mo; *P* = .41) or remission duration probability (38.6 vs not reached vs 10.2 mo; *P* = .24) noted between the 3 arms. 51% of patients in the hyper-CVAD based group were bridged to HCT, compared to 49% of patients in the tagraxofusp group and 38% in the other regimens group, respectively (*P* = .455). This study suggests a continued role for hyper-CVAD based regimens in the targeted-therapy era.

***Venetoclax-Based Regimens***

The antiapoptotic protein B-cell leukemia/lymphoma-2 (BCL2) is overexpressed in a majority of patients with BPDCN.[391] Venetoclax is an oral selective BCL2 inhibitor approved in combination with azacitidine, decitabine, or low dose cytarabine (LDAC) for the treatment of newly-diagnosed AML in patients $\geq$ 75 years or for those who are otherwise not candidates for intensive remission induction therapy.[437] In vitro, BPDCN cells were found to be uniformly sensitive to venetoclax in a study that measured direct cytotoxicity, apoptosis assays, and dynamic BH3 profiling.[438]

A retrospective study assessed the efficacy of venetoclax combinations in a total of 43 patients with R/R myeloid malignancies, including 2 patients with BPDCN.[391] The most common treatment regimens included venetoclax with decitabine (53%), azacitidine (19%), and LDAC (19%). Patients had been previously treated with a median of 3 prior lines of therapy, including allogeneic HCT in 12% of patients. While ORR was seen in 21% of patients, neither of the 2 patients with BPDCN that were evaluated achieved a response by formal criteria, though one patient had a major response by PET/CT, bone marrow blast reduction of >50%, and improvement in cutaneous lesions. The other patient with BPDCN also had a significant improvement in cutaneous lesions. All patients who received venetoclax combination therapy experienced grade 3 or higher neutropenia and 72% developed a grade 3 or higher infection, most commonly pneumonia, bacteremia, cellulitis, invasive fungal infections, and urinary tract infections. All patients were given allopurinol for tumor lysis syndrome prophylaxis, and none developed hyperuricemia that

required rasburicase.[391] Venetoclax in combination with hypomethylating agents appears to have efficacy in BPDCN, but larger and more formalized studies are necessary to confirm these observations.

***Hematopoietic Stem Cell Transplantation***

Due to the rarity of BPDCN, there have been limited established standardized therapeutic approaches.[439] HCT seems to generate durable remissions, especially if given in first CR, as indicated by the studies discussed in the chemotherapy section, as well as others.[416,419,431,435,439,440] However, it is worth noting that data are limited to small case series and retrospective registry studies, and larger prospective studies are needed to elucidate the role of HCT in BPDCN.[440]

A retrospective analysis from the Japan Society for Hematopoietic Cell Transplantation aimed to clarify the role of allogeneic HCT or autologous HCT in treating BPDCN.[416] In this analysis, 25 patients were identified, with 14 patients having undergone allogeneic HCT and 11 patients having undergone autologous HCT. All patients who underwent autologous HCT were in first CR, while 12 of the 14 patients who underwent allogeneic HCT were in first CR (2 were not in remission). With a median follow-up of 53.5 months, the OS rates at 4 years for patients who underwent autologous HCT and allogeneic HCT were 82% and 53%, respectively ($P$ = .11) and the PFS rates were 73% and 48%, respectively ($P$ = .14). The data suggest that receiving autologous HCT in first CR may substantially enhance survival. OS outcomes in the allogeneic HCT subgroup did not differ significantly between myeloablative conditioning (MAC) and RIC regimens.

A North American multicenter retrospective study analyzed the outcomes of BPDCN patients treated with allogeneic HCT (n = 37) or autologous HCT (n = 8).[440] Allogeneic HCT recipients had a 1-year and 3-year OS of 68% (95% CI, 49%–81%) and 58% (95% CI, 38%–75%), respectively. Receiving allogeneic HCT in first CR yielded improved 3-year OS versus allogeneic HCT not in first CR [74% (95% CI, 48%–89%) vs. 0, $P$ < .0001], and outcomes were not impacted by conditioning type (MAC vs RIC). The 1-year OS for autologous HCT recipients was 11% (95% CI, 8%–50%).

A more recent retrospective study evaluated 162 adults with BPDCN that underwent first HCT (allogeneic HCT, n = 146; autologous HCT, n = 16), 78% of whom were in first CR.[441] Among the allogeneic HCT group, 54% received MAC, 46% received RIC, and 59% received in-vivo T-cell depletion (TDC). Total body irradiation (TBI) was used in 61% of MAC transplants and 26% of RIC transplants. Comparable one-year OS and PFS rates were seen following allogeneic and autologous HCT (OS: 66 vs 70%; PFS: 62% vs 66%). TBI as the conditioning backbone in allogeneic HCT led to significant improvements in OS and PFS compared to all other conditioning regimens. Adjusted 2-year PFS for MAC with TBI was 95% compared to 82% for MAC without TBI, 41% for RIC with TBI, and 60% for RIC without TBI, respectively.

***NCCN Recommendations***

For patients who are candidates for intensive remission induction therapy, the panel recommends tagraxofusp-ersz as the preferred option, and other options include AML-type (standard-dose cytarabine plus anthracycline using 7+3), ALL-type (hyper-CVAD), and lymphoma-type (CHOP) regimens. If CNS disease is documented at diagnosis, IT chemotherapy should also be given. If CNS disease is not present at diagnosis, prophylactic IT chemotherapy is strongly encouraged.

Tagraxofusp-ersz should be administered as an IV infusion at 12 µg/kg over 15 minutes once daily on days 1 to 5 of each 21-day cycle. Alternatively, 5 doses can be administered over a 10-day period, if needed for dose delays. It is important to note that patients must have a baseline serum albumin of 3.2 g/dL or higher to be able to start treatment with this agent. The most serious side effect associated with tagraxofusp is capillary leak syndrome, which can occur during the first cycle of treatment

and can be life-threatening.[422] A decrease in serum albumin during the first days of treatment seems to be the most consistent predictor of capillary leak syndrome.[422] Management includes delaying or withholding additional tagraxofusp doses, administering IV albumin according to pre-specified measures, administering glucocorticoids, and close management of volume status.[422] The panel recommends replacing serum albumin if <3.5 g/dL or if there is a reduction of ≥0.5 from baseline. The panel also recommends premedication with an H1-histamine antagonist, acetaminophen, corticosteroid, and H2-histamine antagonist prior to each infusion to help reduce the risk of hypersensitivity reaction.

With all treatment options, if CR is observed, allogeneic HCT or autologous HCT should be considered. If tagraxofusp-erzs was given as an initial treatment and HCT is not feasible, additional cycles of tagraxofusp-erzs should be continued until disease progression. If disease progresses or does not respond to induction therapy, patients should be considered for a clinical trial (preferred), or regimens used for R/R disease.

For patients with low performance and/or nutritional status (ie, serum albumin <3.2 g/dL) or for those who are not candidates for intensive remission induction therapy or tagraxofusp-ersz, treatment options are limited. If disease is localized or isolated to cutaneous involvement, palliative treatment options include surgical excision or focal radiation. If disease is systemic, palliative options include low-intensity therapy with venetoclax-based regimens, steroids, and supportive care.

### Postremission Surveillance for BPDCN

Following completion of consolidation therapy, it is recommended to monitor a CBC, including platelets, every 1 to 3 months for the first 2 years, then every 3 to 6 months thereafter for up to 5 years. Bone marrow evaluation should be performed only if cytopenias develop or if peripheral smear is abnormal, rather than as routine surveillance at fixed intervals, unless the bone marrow evaluation is being performed as part of a clinical research protocol. For patients with prior evidence of extramedullary disease, a repeat PET/CT scan is recommended. In addition, routine thorough skin exams with a re-biopsy should occur for any suspicious skin or extramedullary lesions.

### Management of Relapsed/Refractory BPDCN

Upon relapse, the NCCN AML Panel recommends evaluating for CNS disease and administering IT chemotherapy prophylaxis.[423] Management options for R/R BPDCN include clinical trial (preferred), tagraxofusp-ersz (preferred, if not already used),[422] chemotherapy (if not already given), local radiation to isolated lesions, systemic steroids, or venetoclax-based regimens.[391,438] During administration of any treatment option, a donor search should also be started at first relapse in appropriate patients if no sibling donor has been identified.

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