National Comprehensive Cancer Network®

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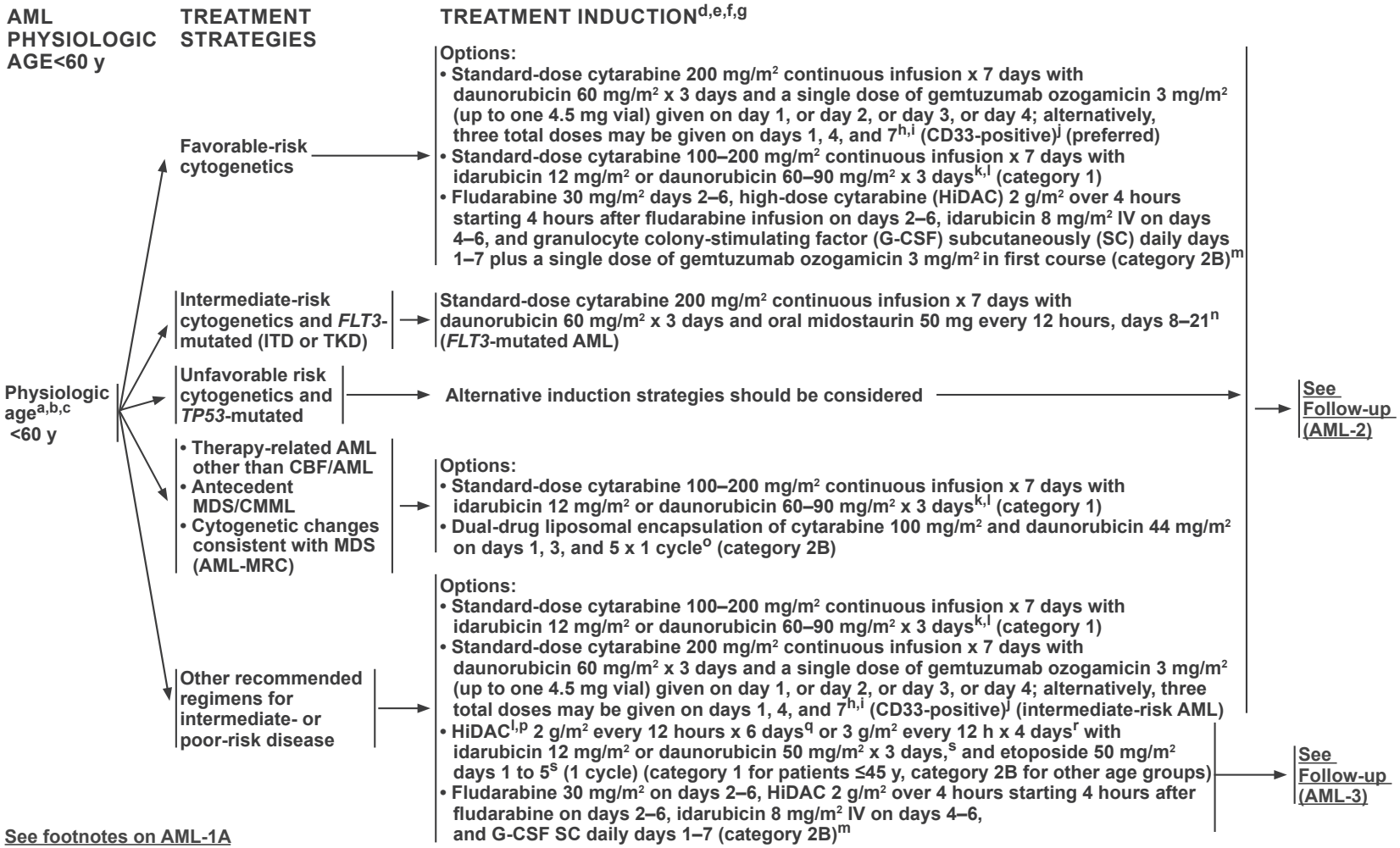
NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®)

Acute Myeloid Leukemia

Overall management of Acute Myeloid Leukemia is described in the full NCCN Guidelines® for Acute Myeloid Leukemia. Visit NCCN.org to view the complete library of NCCN Guidelines.



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 TREATMENT INDUCTION (PHYSIOLOGICAGE <60 YEARS)

[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 apheresis, hydroxyurea, and/or a single dose of cytarabine (1–2 g). Prompt institution of definitive therapy is essential.

[b] Poor performance status and a comorbid medical condition, in addition to age, are factors that influence ability to tolerate standard induction therapy.

[c] Patients with CBF-AML and core abnormalities may benefit from the addition of gemtuzumab ozogamicin. Consider screening with fluorescence in situ hybridization (FISH) to identify translocations/abnormalities associated with CBF-AML.

[d] See Principles of Supportive Care for AML (AML-E).

[e] See Monitoring During Therapy (AML-F).

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

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

[h] Burnett AK, et al. J Clin Oncol 2011;29:369-377. Meta-analyses showing an advantage with gemtuzumab ozogamicin have included other dosing schedules; Hills RK, et al. Lancet Oncol 2014;15:986-996.

[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 complete response rates and overall survival 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] Burnett AK, et al. J Clin Oncol 2013;31:3360-3368.

[n] This regimen is for *FLT3* mutation-positive AML (both ITD and TKD mutations). While midostaurin was 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] 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.

[p] The use of high-dose cytarabine for induction outside the setting of a clinical trial is still controversial. While the remission rates are the same for standard- and high-dose cytarabine, two studies have shown more rapid marrow blast clearance after one cycle of high-dose therapy. Kern W and Estey EH. Cancer 2006;107:116-124. However, one study showed that high-dose cytarabine may improve the outcome for younger patients. Willemze R, et al. J Clin Oncol 2014;32:219-228.

[q] Weick JK, et al. Blood 1996;88:2841-2851.

[r] Bishop JF, et al. Blood 1996;87:1710-1717.

[s] Willemze R, et al. J Clin Oncol 2014;32:219-228.

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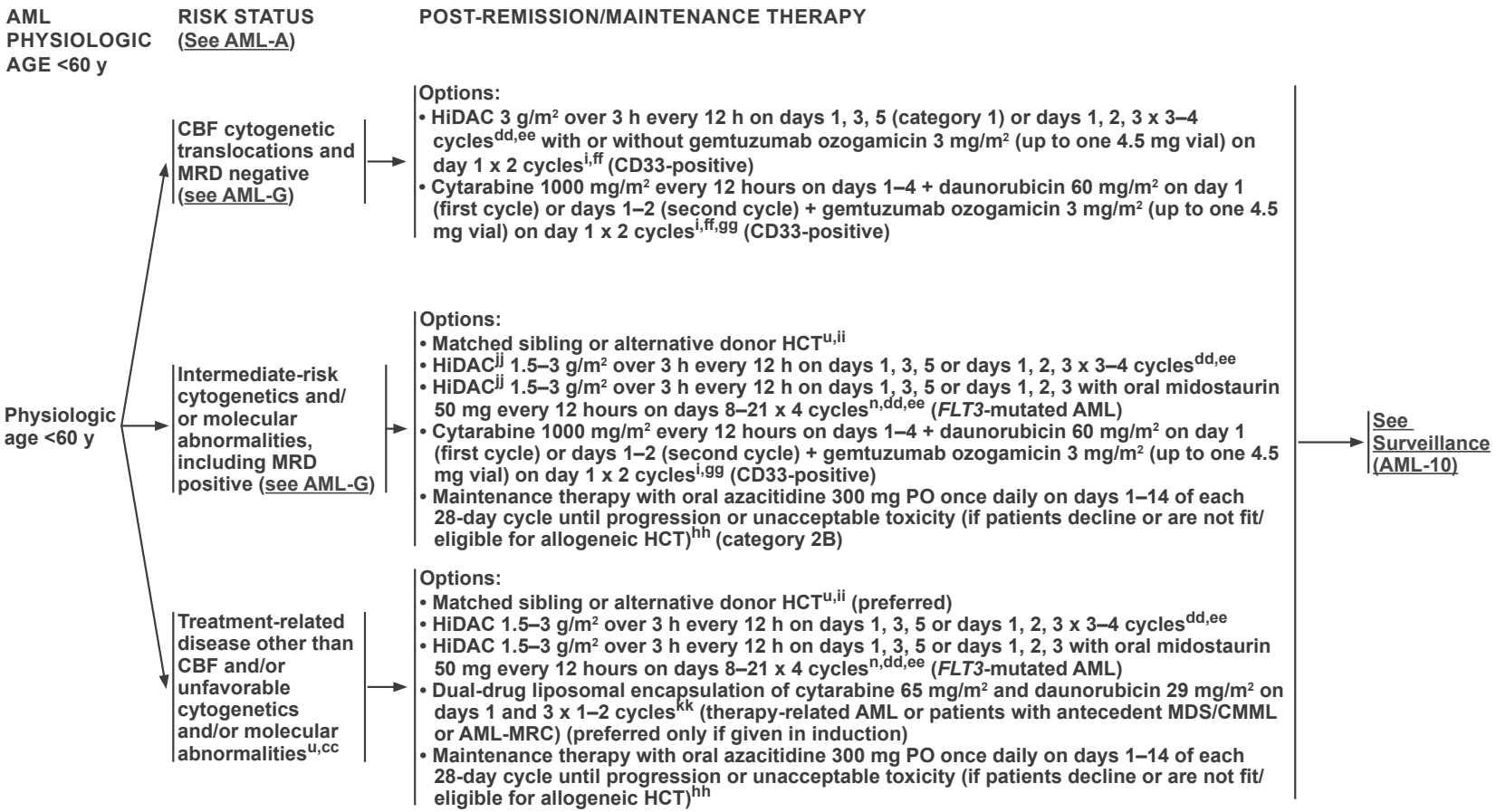

See footnotes on AML-4A

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FOOTNOTES FOR POST-REMISSION/MAINTENANCE THERAPY (PHYSIOLOGIC AGE <60 YEARS)

[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.

[n] This regimen is for *FLT3* mutation-positive AML (both ITD and TKD mutations). While midostaurin was 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.

[u] 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 induction failure, alternative therapy to achieve remission is encouraged prior to HCT.

[cc] *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.

[dd] Mayer RJ, et al. N Engl J Med 1994;331:896-903; Jaramillo S, et al. Blood Cancer J 2017;7:e564.

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

[ff] Meta-analyses showing an advantage with gemtuzumab ozogamicin have included other dosing schedules. Hills RK, et al. Lancet Oncol 2014;15:986-996.

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

[hh] This is a maintenance therapy and is not intended to replace consolidation chemotherapy, which can be curative in some cases. In addition, fit patients 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 younger patients or those with CBF-AML; it was restricted to patients ≥55 years of age 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. Blood 2019;134 (Suppl_2):LBA-3.

[ii] Patients may require at least one cycle of high-dose cytarabine 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.

[jj] 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 intermediate-risk cytogenetics.

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

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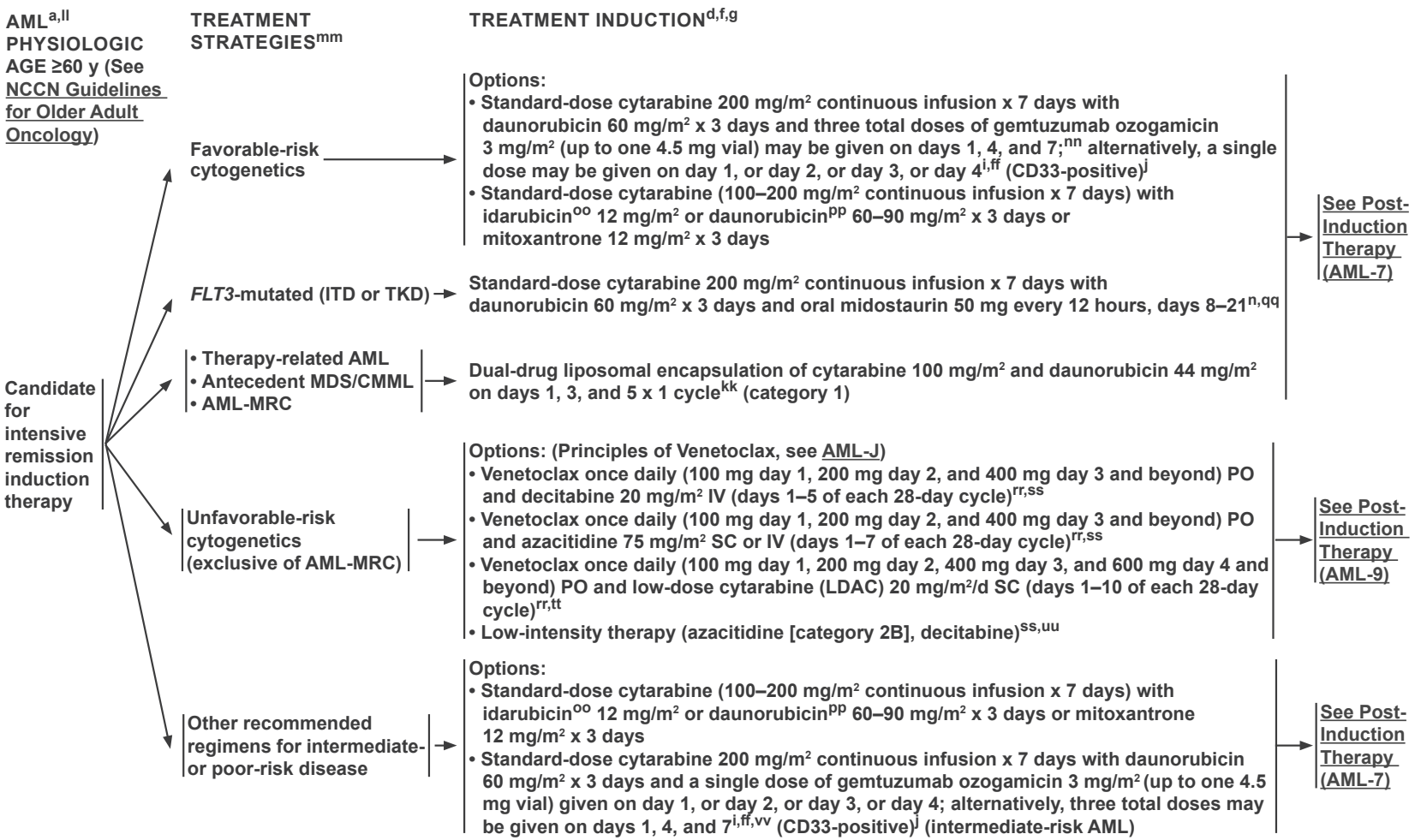

See footnotes on AML-5A

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FOOTNOTES FOR TREATMENT INDUCTION (PHYSIOLOGICAGE ≥60 YEARS)

[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 apheresis, hydroxyurea, and/or a single dose of cytarabine (1–2 g). Prompt institution of definitive therapy is essential.

[d] See Principles of Supportive Care for AML (AML-E).

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

[g] See General Considerations and Supportive Care for Patients 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 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] This regimen is for *FLT3* mutation-positive AML (both ITD and TKD mutations). While midostaurin was 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.

[ff] Meta-analyses showing an advantage with gemtuzumab ozogamicin have included other dosing schedules. Hills RK, et al. Lancet Oncol 2014;15:986-996.

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

[ll] There is a web-based scoring tool available to evaluate the probability of complete response and early death after standard induction therapy in elderly patients with AML: http://www.aml-score.org/. Krug U, et al. Lancet 2010;376:2000-2008. A web-based tool to predict CR and early death can be found at: https://www.fhcrc-research.org/TRM/Default.aspx?GUID=1358501B-C922-4422-84F0-0E6C67D8F266 and Walter RB, et al. J Clin Oncol 2011;29:4417-4423.Factors in decisions about fitness for induction chemotherapy include age, performance status, functional status, and comorbid conditions. See NCCN Guidelines for Older Adult Oncology.

[mm] Patients with *TP53* mutations are a group with poor prognosis, and should be considered for enrollment in clinical trials.

[nn] Castaigne S, et al. Lancet 2012;379:1508-1516.

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

[pp] The complete response rates and 2-year overall survival 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).

[qq] The RATIFY trial studied patients aged 18–60 y. An extrapolation of the data suggests that older patients 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.

[rr] This regimen may be continued for patients who demonstrate clinical improvement (CR/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; Wei A, et al. Haematologica 2017; Abstract S473; DiNardo CD, Blood 2019;133:7-17; DiNardo CD, et al. N Engl J Med 2020;383:617-629.

[ss] Patients who have progressed to AML from MDS after significant exposure to hypomethylating agents (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.

[tt] Wei AH, et al. J Clin Oncol 2019;37:1277-1284.

[uu] 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.

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

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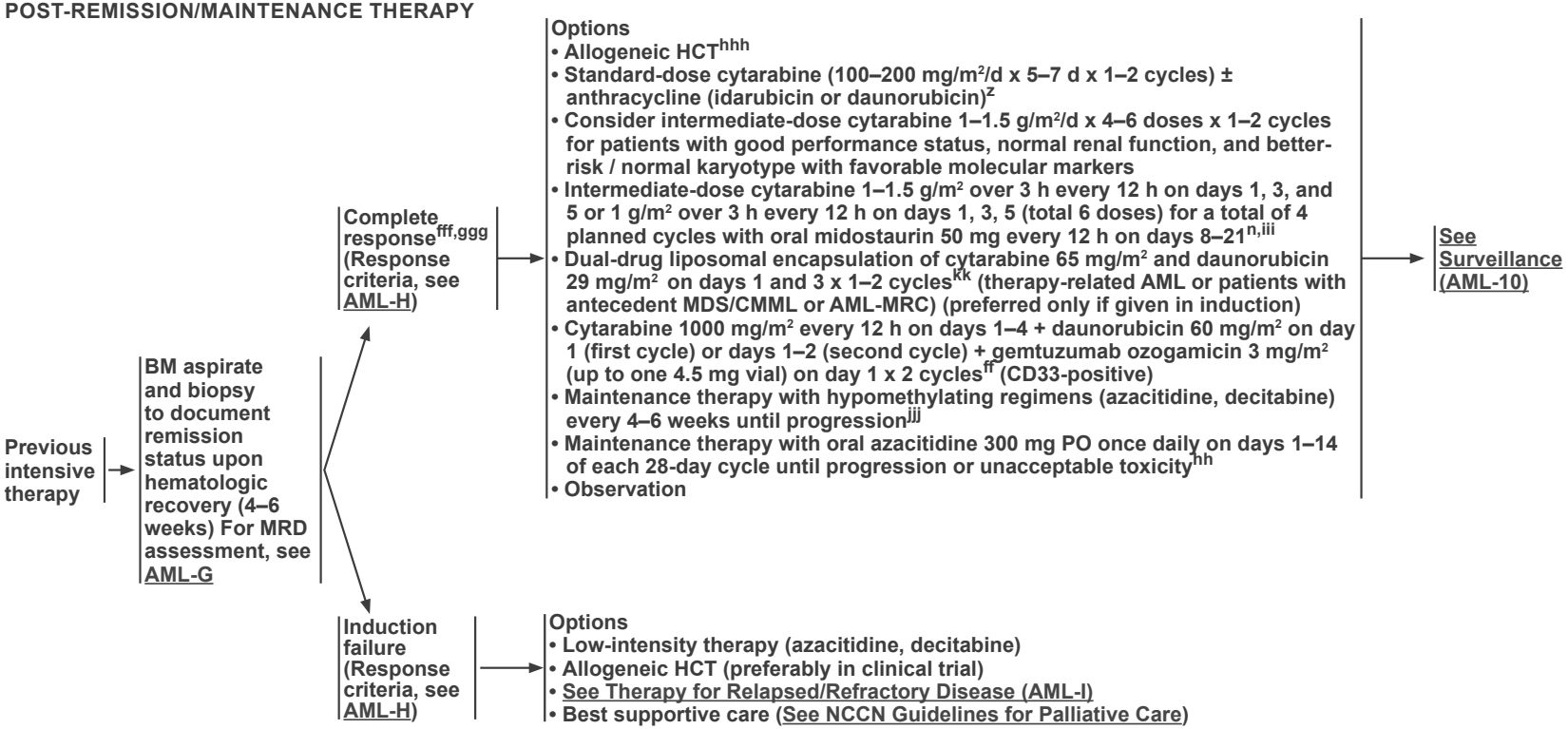
AML PHYSIOLOGIC AGE ≥60 y
POST-REMISSION/MAINTENANCE THERAPY



See footnotes on AML-8A

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FOOTNOTES FOR POST-REMISSION/MAINTENANCE THERAPY (PHYSIOLOGIC AGE ≥60 YEARS)

[n] This regimen is for *FLT3* mutation-positive AML (both ITD and TKD mutations). While midostaurin was 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.

[z] 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.

[ff] Meta-analyses showing an advantage with gemtuzumab ozogamicin have included other dosing schedules. Hills RK, et al. Lancet Oncol 2014;15:986-996.

[hh] This is a maintenance therapy and is not intended to replace consolidation chemotherapy, which can be curative in some cases. In addition, fit patients with intermediate- and/or adverse-risk cytogenetics may benefit from HCT in first CR, and there is no data to suggest that maintenance therapy with oral azacitidine can replace HCT. The panel also notes that the trial did not include younger patients or those with with CBF-AML; it was restricted to patients ≥55 years of age 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. Blood 2019;134 (Suppl_2):LBA-3.

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

[fff] Patients in remission may be screened with LP if initial WBC count >40,000/mcL or monocytic histology. See Evaluation and Treatment of CNS Leukemia (AML-B).

[ggg] HLA typing should be used for patients considered to be strong candidates for allogeneic transplantation.

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

[iii] Alternate administration of intermediate-dose cytarabine may also be used. Sperr WG, et al. Clin Cancer Res 2004;10:3965-3971. The RATIFY trial studied patients aged 18–60 y. An extrapolation of the data suggests that older patients 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.

[jjj] An option for patients who had achieved a remission with a more intensive regimen but had regimen-related toxicity that prevented them from receiving more conventional consolidation. Huls G, et al. Blood 2019;133:1457-1464.

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Provided by Jazz Pharmaceuticals:

VYXEOS® (daunorubicin and cytarabine) IMPORTANT SAFETY INFORMATION

WARNING: DO NOT INTERCHANGE WITH OTHER DAUNORUBICIN AND/OR CYTARABINE-CONTAINING PRODUCTS

VYXEOS has different dosage recommendations than daunorubicin hydrochloride injection, cytarabine injection, daunorubicin citrate liposome injection, and cytarabine liposome injection. Verify drug name and dose prior to preparation and administration to avoid dosing errors.

Contraindications
VYXEOS is contraindicated in patients with a history of serious hypersensitivity reactions to cytarabine, daunorubicin, or any component of the formulation.

Warnings and Precautions

Hemorrhage
Serious or fatal hemorrhage events, including fatal CNS hemorrhages, associated with prolonged thrombocytopenia, have occurred with VYXEOS (daunorubicin and cytarabine). The overall incidence (grade 1-5) of hemorrhagic events was 74% in the VYXEOS arm and 56% in the control arm. The most frequently reported hemorrhagic event was epistaxis (36% in VYXEOS arm and 18% in control arm). Grade 3 or greater events occurred in 12% of VYXEOS-treated patients and in 8% of patients in the control arm. Fatal treatment-emergent CNS hemorrhage not in the setting of progressive disease occurred in 2% of patients in the VYXEOS arm and in 0.7% of patients in the control arm. Monitor blood counts regularly and administer platelet transfusion support as required.

Cardiotoxicity
VYXEOS contains daunorubicin, which has a known risk of cardiotoxicity. This risk may be increased in patients with prior anthracycline therapy, preexisting cardiac disease, previous radiotherapy to the mediastinum, or concomitant use of cardiotoxic drugs. Assess cardiac function prior to VYXEOS treatment and repeat prior to consolidation and as clinically required. Discontinue VYXEOS in patients with impaired cardiac function unless the benefit of initiating or continuing treatment outweighs the risk. VYXEOS is not recommended in patients with cardiac function that is less than normal.

Total cumulative doses of non-liposomal daunorubicin greater than 550 mg/m^2 have been associated with an increased incidence of drug-induced congestive heart failure. The tolerable limit appears lower (400 mg/m^2) in patients who received radiation therapy to the mediastinum. Calculate the lifetime cumulative anthracycline exposure prior to each cycle of VYXEOS. VYXEOS is not recommended in patients whose lifetime anthracycline exposure has reached the maximum cumulative limit.

Hypersensitivity Reactions
Serious or fatal hypersensitivity reactions, including anaphylactic reactions, have been reported with daunorubicin and cytarabine. Monitor patients for hypersensitivity reactions. If a mild or moderate hypersensitivity reaction occurs, interrupt or slow the rate of infusion with VYXEOS and manage symptoms. If a severe or life-threatening hypersensitivity reaction occurs, discontinue VYXEOS permanently, treat the symptoms, and monitor until symptoms resolve.

Copper Overload
VYXEOS contains copper. Consult with a hepatologist and nephrologist with expertise in managing acute copper toxicity in patients with Wilson's disease treated with VYXEOS. Monitor total serum copper, serum non-ceruloplasmin-bound copper, 24-hour urine copper levels, and serial neuropsychological examinations during VYXEOS treatment in patients with Wilson's disease or other copper-related metabolic disorders. Use only if the benefits outweigh the risks. Discontinue in patients with signs or symptoms of acute copper toxicity.

Tissue Necrosis
Daunorubicin has been associated with severe local tissue necrosis at the site of drug extravasation. Administer VYXEOS by the intravenous route only. Confirm patency of intravenous access before administration. Do not administer by intramuscular or subcutaneous route.

Embryo-Fetal Toxicity
VYXEOS can cause embryo-fetal harm when administered to a pregnant woman. Patients should avoid becoming pregnant while taking VYXEOS. If VYXEOS is used during pregnancy or if the patient becomes pregnant while taking VYXEOS, apprise the patient of the potential risk to a fetus. Advise females and males of reproductive potential to use effective contraception during treatment and for 6 months following the last dose of VYXEOS.

MOST COMMON ADVERSE REACTIONS
The most common adverse reactions (incidence ≥25%) were hemorrhagic events (74%), febrile neutropenia (70%), rash (56%), edema (55%), nausea (49%), mucositis (48%), diarrhea (48%), constipation (42%), musculoskeletal pain (43%), fatigue (39%), abdominal pain (36%), dyspnea (36%), headache (35%), cough (35%), decreased appetite (33%), arrhythmia (31%), pneumonia (31%), bacteremia (29%), chills (27%), sleep disorders (26%), and vomiting (25%).