Taipei Veterans General Hospital Practice Guidelines Hematology

Leukemia

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Taipei Veterans General Hospital Practice Guidelines Hematology

Acute Myeloid Leukemia

Acute Myeloid Leukemia

ECOG PERFORMANCE STATUS	
Grade	ECOG
0	Fully active, able to carry on all pre-disease performance without restriction
1	Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, e.g., light house work, office work
2	Ambulatory and capable of all selfcare but unable to carry out any work activities. Up and about more than 50% of waking hours
3	Capable of only limited selfcare, confined to bed or chair more than 50% of waking hours
4	Completely disabled. Cannot carry on any selfcare. Totally confined to bed or chair
5	Dead

Oken, M.M., Creech, R.H., Tormey, D.C., Horton, J., Davis, T.E., McFadden, E.T., Carbone, P.P.: Toxicity And Response Criteria Of The Eastern Cooperative Oncology Group. Am J Clin Oncol 5:649-655, 1982

Acute Myeloid Leukemia

- Grading for adverse effect from chemotherapy:

  CTCAE 5.0/https://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm

Grades

Grade refers to the severity of the AE. The CTCAE displays Grades 1 through 5 with unique clinical descriptions of severity for each AE based on this general guideline:

Grade 1 Mild; asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated.

Grade 2 Moderate; minimal, local or noninvasive intervention indicated; limiting age-appropriate instrumental ADL*.

Grade 3 Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self care ADL**.

Grade 4 Life-threatening consequences; urgent intervention indicated.

Grade 5 Death related to AE.

Acute Myeloid Leukemia

EVALUATION FOR AML

- History and physical (H&P)
- Complete blood count (CBC), platelets, differential, comprehensive metabolic panel, 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 cytogenetic analyses (karyotype +/- FISH) (See AML-A)
- Molecular analyses (ex. *ASXL1*, c-*KIT*, *FLT3* [ITD and TKD], *NPM1*, *CEBPA* [biallelic], *IDH1*, *IDH2*, *RUNX1*, *TP53*, and other mutations)[a] (See AML-A)
- Comprehensive pathology report, including diagnosis of AML with recurrent cytogenetics vs. AML 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)
- 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 to thorax
- Consider early integration of palliative care

DIAGNOSTIC STUDIES (WHO 2016)

Multidisciplinary diagnostic studies[d,e]

DIAGNOSIS[d,e,f,g]

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)

Acute myeloid leukemia (AML):
To appropriately stratify available intensive therapy options, expedite test results of molecular and cytogenetic analyses for immediately actionable mutations or chromosomal abnormalities (eg, *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

→ See AML Risk Stratification and Treatment Recommendations (AML-1)

Myelodysplastic syndromes (MDS)

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

See footnotes on EVAL-1A

Note: All recommendations are category 2A unless otherwise indicated.
Clinical Trials: Participation in clinical trials is encouraged in selected cases.

Acute Myeloid Leukemia

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 comprehensive 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 marrow 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 morphologically detectable, circulating leukemic blasts.

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

[d] 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 high- grade MDS may allow enrollment of patients with AML-MDS.

[e] When presented with rare cases such as acute leukemias of ambiguous lineage including mixed phenotype acute leukemias (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. AML patients should preferably be managed at experienced leukemia centers where clinical trials may be more available.

[g] Patients who present with isolated extramedullary disease (myeloid sarcoma) should be treated with systemic therapy. Local therapy (radiation therapy [RT] or surgery [rare cases]) may be used for residual disease. Allogeneic HSCT may be considered in selected cases. See Principles of Radiation Therapy (AML-C).

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

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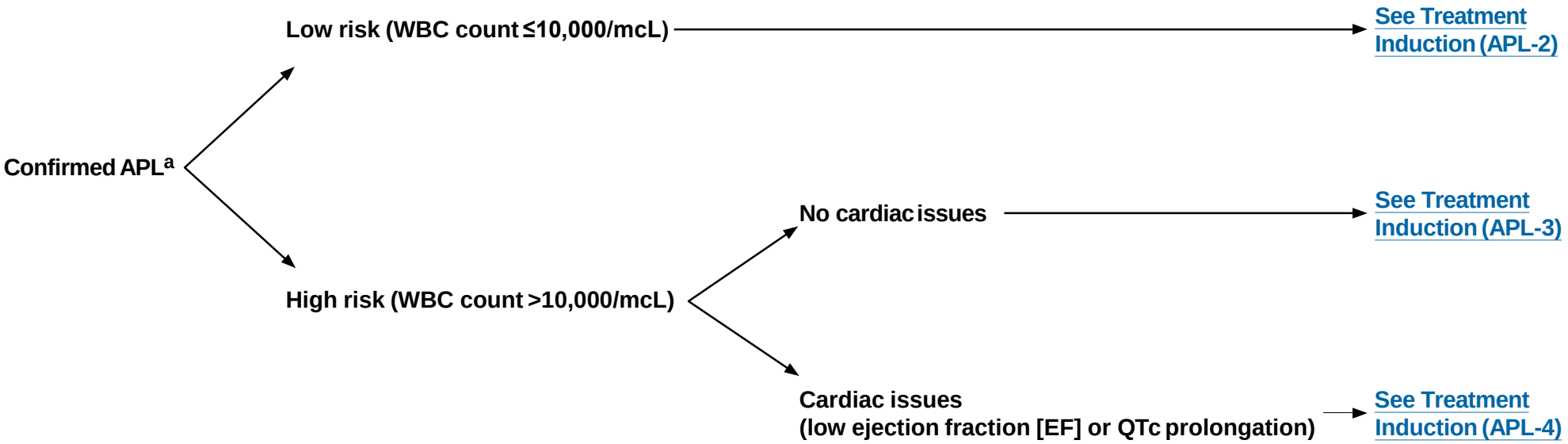
Clinical Trials: Participation in clinical trials is encouraged in selected cases.

Acute Promyelocytic Leukemia

APL CLASSIFICATION AND TREATMENT RECOMMENDATIONS



[a] Therapy-related APL is treated the same as de novo APL.

Note: All recommendations are category 2A unless otherwise indicated.
Clinical Trials: Participation in clinical trials is encouraged in selected cases.

Acute Promyelocytic Leukemia

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

Preferred Regimens

ATRA[f] 45 mg/m^2 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, ANC >1,000), proceed with consolidation.
  BM aspirate and biopsy may be considered to document morphologic remission[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 morphologic remission[l,m] before proceeding with consolidation

or

ATRA[f] 45 mg/m^2 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 morphologic remission[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 morphologic remission[l,m] before proceeding with consolidation

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

ATRA[f] 45 mg/m^2 in 2 divided doses daily + idarubicin 12 mg/m^2 on days 2, 4, 6, 8[j] (category 1)

→ At count recovery, proceed with consolidation[m,n]

CONSOLIDATION THERAPY[m,n]

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/m^2/d for 2 weeks every 4 weeks for a total of 7 cycles[h] (category 1)

First 3 consolidation cycles = 56-day cycles:
ATRA 45 mg/m^2/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/m^2/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]

ATRA 45 mg/m^2 x 15 days + idarubicin 5 mg/m^2 x 4 days x 1 cycle, then ATRA x 15 days + mitoxantrone 10 mg/m^2/d x 3 days x 1 cycle, then ATRA x 15 days + idarubicin 12 mg/m^2 x 1 day x 1 cycle (category 1)[j]

→ See Post-Consolidation Therapy (APL-5)

Note: All recommendations are category 2A unless otherwise indicated.
Clinical Trials: Participation in clinical trials is encouraged in selected cases.

Acute Promyelocytic Leukemia

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 of 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).
[h] Lo-Coco F, et al. N Engl J Med 2013;369:111-121. Begin prophylaxis with prednisone through completion of induction. 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.
[l] If no evidence of morphologic disease (ie, absence of blasts and 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 marrow 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.

Note: All recommendations are category 2A unless otherwise indicated.
Clinical Trials: Participation in clinical trials is encouraged in selected cases.

Acute Promyelocytic Leukemia

APL TREATMENT INDUCTION (HIGH RISK)[b,c,d,o,p]
(FOR PATIENTS WITH CARDIAC ISSUES, SEE APL-4)

CONSOLIDATION THERAPY[n]
See references for details on regimens including maintenance therapy.

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)[q]

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

→ **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 2weeks x 3 + arsenic trioxide 0.15 mg/kg/d x 5 days for 5 weeks x 1 cycle[q,w,x]**

Other Recommended Regimens[s]

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)[t]

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

→ **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[t,x]**

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[u]

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

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

or

ATRA[f] 45 mg/m² in 2 divided doses daily + idarubicin 12 mg/m² on days 2, 4, 6, 8[j]

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

→ **ATRA 45 mg/m² x 15 days + idarubicin 5 mg/m² and cytarabine 1 g/m² x 4 days x 1 cycle, then ATRA x 15 days + mitoxantrone 10 mg/m²/d x 5 days 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,x]**

→ **See Post-Consolidation Therapy (APL-5)**

See footnotes on APL-3A

Note: All recommendations are category 2A unless otherwise indicated.
Clinical Trials: Participation in clinical trials is encouraged in selected cases.

Acute Promyelocytic Leukemia

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/m2) 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).
[j] Sanz MA, et al. Blood 2010;115:5137-5146.
[l] If no evidence of morphologic disease (ie, absence of blasts and 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 marrow 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] 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.
[p] 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. 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.
[q] Iland HJ, et al. Blood 2012;120:1570-1580.
[s] No arsenic is included in induction if unavailable or contraindicated.
[t] Powell BL, et al. Blood 2010;116:3751-3757.
[u] Adès L, et al. Blood 2008;111:1078-1084.
[v] Breccia M, et al. Br J Haematol 2003;120:266-270.
[w] Although the original regimen included high-dose cytarabine as second consolidation, some investigators recommend using high-dose cytarabine early for CNS prophylaxis, especially for patients not receiving IT chemotherapy.
[x] Consider IT chemotherapy (eg, 2 doses for each consolidation cycle) as an option for CNS prophylaxis.
[y] Dose adjustment of cytarabine may be needed for older patients or patients with renal dysfunction.

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Clinical Trials: Participation in clinical trials is encouraged in selected cases.

Acute Promyelocytic Leukemia

APL TREATMENT INDUCTION (HIGH RISK)[b,c,d,o]
IN PATIENTS WITH CARDIAC ISSUES
(FOR PATIENTS WITHOUT CARDIAC ISSUES, SEE APL-3)

CONSOLIDATION THERAPY[n]

Low Ejection Fraction (unless gemtuzumab ozogamicin available, treatment regimen should be tailored individually)

Prolonged QTc

ATRA[f] 45 mg/m² in 2 divided doses daily + daunorubicin 60 mg/m² x 3 days + cytarabine 200 mg/m² x 7 days[u]
→ **BM aspirate and biopsy at day 28 to document remission,[m] consider LP before proceeding with consolidation[v]**
→ **Daunorubicin 60 mg/m² x 3 days + cytarabine 200 mg/m² x 7 days x 1 cycle, then cytarabine 2 g/m² (age <50) or 1.5 g/m² (age 50–60) every 12 h x 5 days[w,y] + daunorubicin 45 mg/m² x 3 days x 1 cycle + 5 doses of IT chemotherapy[u]**

or

ATRA[f] 45 mg/m² in 2 divided doses daily + idarubicin 12 mg/m² on days 2, 4, 6, 8[j]
→ **BM aspirate and biopsy at day 28 to document remission,[m] consider LP before proceeding with consolidation[v]**
→ **ATRA 45 mg/m² x 15 days + idarubicin 5 mg/m² and cytarabine 1 g/m² x 4 days x 1 cycle, then ATRA x 15 days + mitoxantrone 10 mg/m²/d x 5 days 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]**

→ **See Post-Consolidation Therapy (APL-5)**

See footnotes on APL-4A

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Clinical Trials: Participation in clinical trials is encouraged in selected cases.

Acute Promyelocytic Leukemia

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.
[i] Burnett AK, et al. Lancet Oncol 2015;16:1295-1305.
[j] Sanz MA, et al. Blood 2010;115:5137-5146.
[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] 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.
[u] Adès L, et al. Blood 2008;111:1078-1084.
[v] Breccia M, et al. Br J Haematol 2003;120:266-270.
[w] Although the original regimen included high-dose cytarabine as second consolidation, some investigators recommend using high-dose cytarabine early for CNS prophylaxis, especially for patients not receiving IT chemotherapy.
[y] Dose adjustment of cytarabine may be needed for older patients or patients with renal dysfunction.

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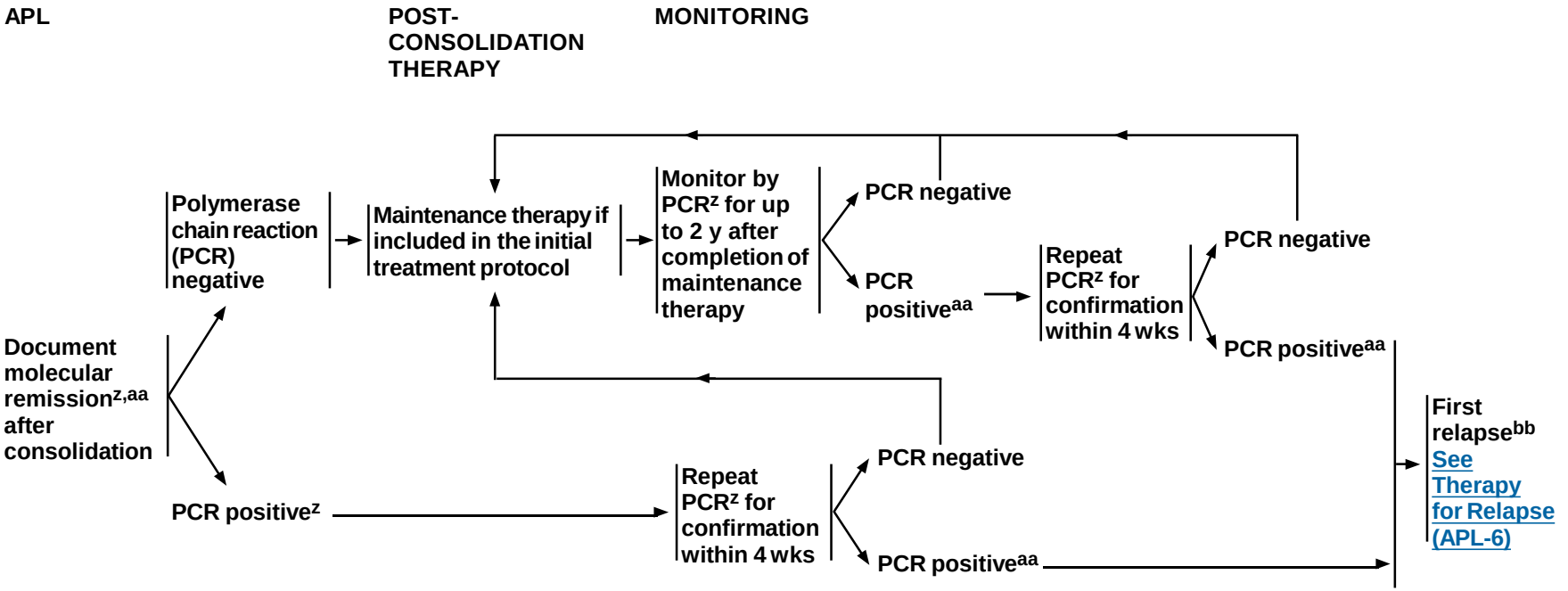
Acute Promyelocytic Leukemia



[z] 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 high-risk patients, 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.

[aa] 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 patient 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.

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

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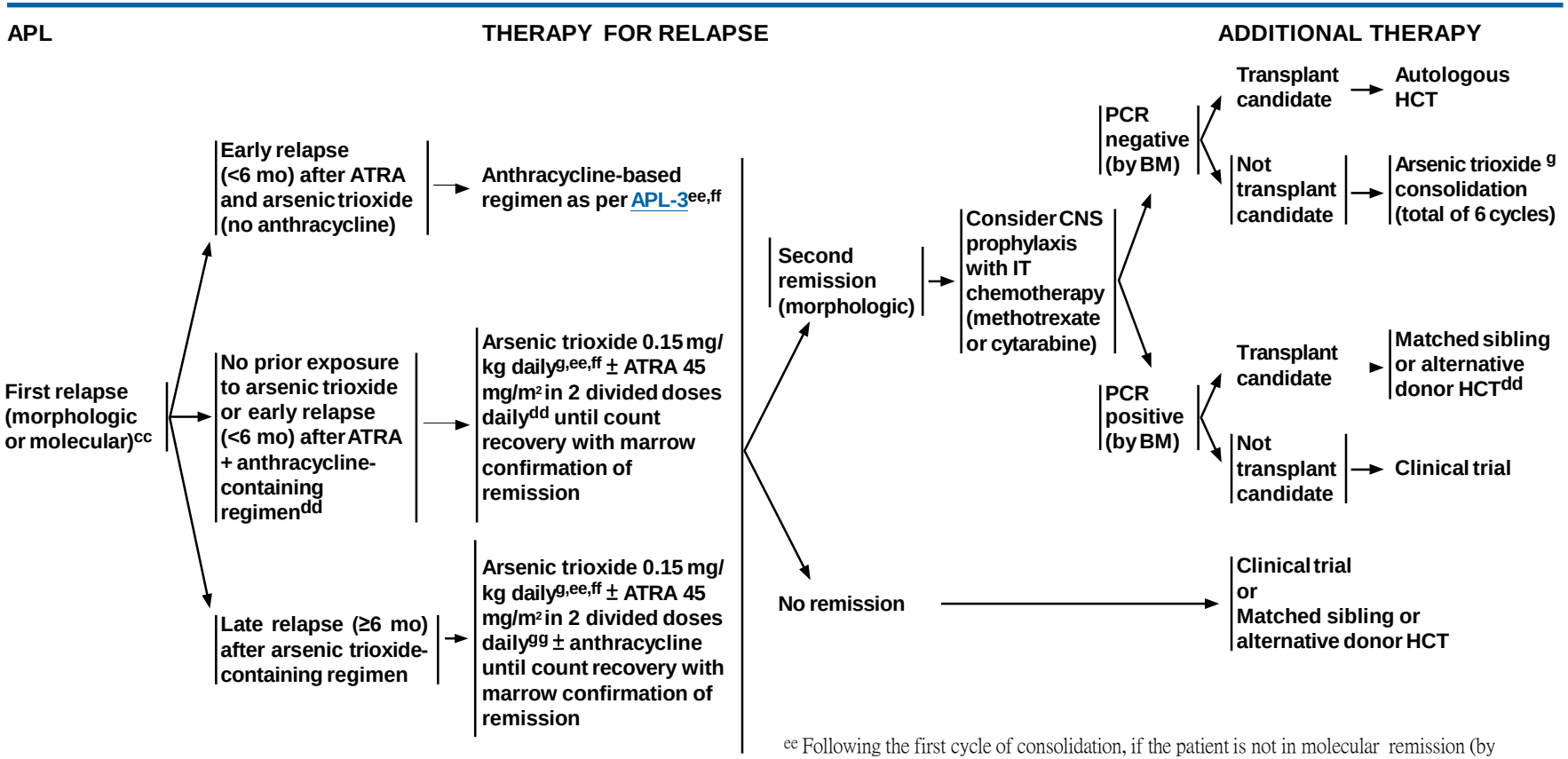
Acute Promyelocytic Leukemia



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).

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

dd Cicconi L, et al. Ann Hematol2018;97:1797-1802.

ee Following the first cycle of consolidation, if the patient is not in molecular remission (by quantitative PCR on marrow 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 to avoid false positives.

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

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

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Acute Promyelocytic Leukemia

PRINCIPLES OF SUPPORTIVE CARE FOR APL[1]

There are variations among institutions, but the following issues are important to consider in the management of patients with 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[2] is not recommended in the routine management of 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:**
  - **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 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. 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.[3,4]**
  - **The following cytoreduction strategies for leukocytosis may be used for differentiation syndrome that is difficult to treat: hydroxyurea, anthracycline.**
- **Arsenic trioxide monitoring:**
  - **Prior to initiating therapy**
    - **Electrocardiogram (ECG) for prolonged QTc interval assessment**
    - **Serum electrolytes (Ca, K, Mg) 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.[5]**
- **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.**

[1] 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.

[2] Daver N, et al. Br J Haematol 2015;168:646-53.
[3] Lo-Coco F, et al. N Engl J Med 2013;369:111-121.
[4] Sanz MA, et al. Blood 2010;115:5137-5146.
[5] Sanz MA, et al. Blood 2019;133:1630-1643.

Note: All recommendations are category 2A unless otherwise indicated.
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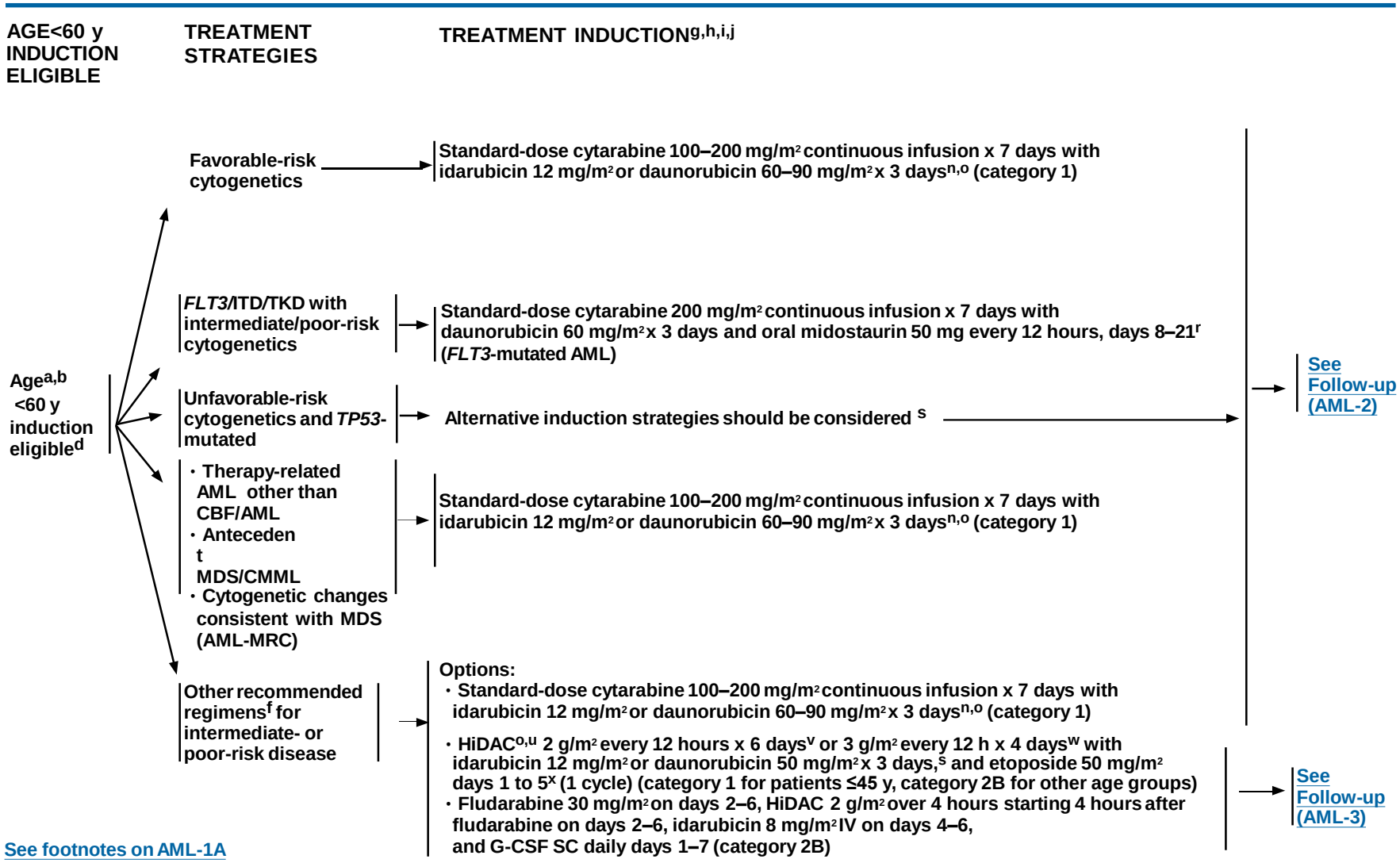
Acute Myeloid Leukemia



See footnotes on AML-1A

Note: All recommendations are category 2A unless otherwise indicated.
Clinical Trials: Participation in clinical trials is encouraged in selected cases.

Acute Myeloid Leukemia

FOOTNOTES FOR TREATMENT INDUCTION ELIGIBLE (AGE <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.

[d] Borlenghi E, et al. J Geriatr Oncol 2021;12:550-556.

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

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

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

[n] 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.

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

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

[r] This regimen is for *FLT3* mutation-positive AML (both ITD and TKD mutations). While midostaurin was not FDAapproved 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.

[s] Outcomes with unfavorable-risk cytogenetics and *TP53*-mutated AML remain poor with conventional induction chemotherapy (Rücker FG, et al. Blood 2012;119:2114-2121). Consider clinical trials, azacitidine/venetoclax (DiNardo CD, et al. N Engl J Med 2020;383:617-629), or a 10-day course of decitabine (Welch JS, et al. N Engl J Med 2016;375:2023-2036).

[u] 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.

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

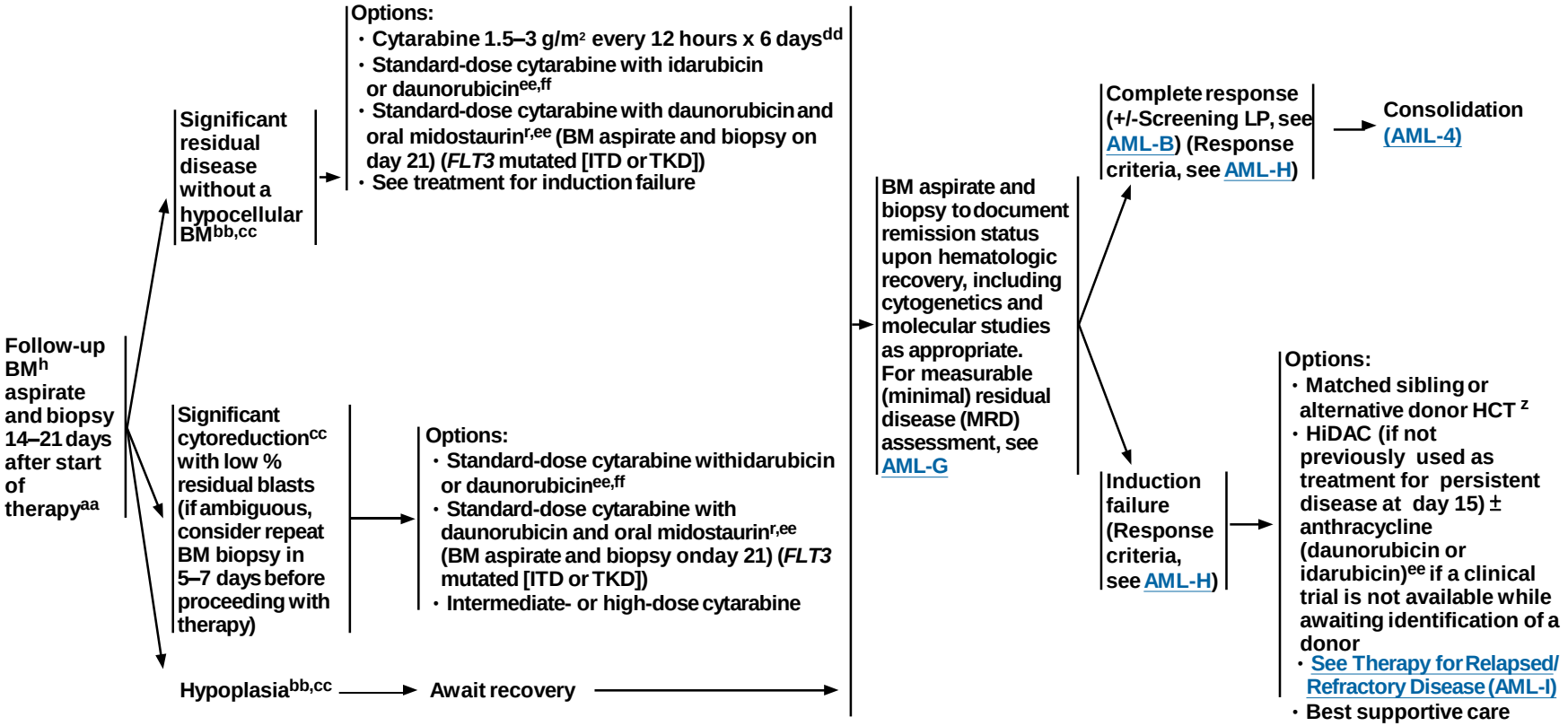
[w] Bishop JF, et al. Blood 1996;87:1710-1717.

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

Note: All recommendations are category 2A unless otherwise indicated.
Clinical Trials: Participation in clinical trials is encouraged in selected cases.

Acute Myeloid Leukemia

AGE <60 y
AFTER STANDARD-DOSE CYTARABINE INDUCTION/RE-INDUCTION[i,y,z]



See footnotes on AML-2A

Note: All recommendations are category 2A unless otherwise indicated.
Clinical Trials: Participation in clinical trials is encouraged in selected cases.

Acute Myeloid Leukemia

FOOTNOTES FOR TREATMENT AFTER STANDARD-DOSE CYTARABINE INDUCTION/RE-INDUCTION (AGE <60 YEARS)

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

[i] 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.

[r] This regimen is for *FLT3* mutation-positive AML (both ITD and TKD mutations). While midostaurin was not FDAapproved 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.

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

[z] 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.

[aa] There are limited prospective data to support this recommendation. Othus M, et al. Leukemia 2016;30:1779-1780.

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

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

[dd] For re-induction, no data are available to show superiority with intermediate or high-dose cytarabine.

[ee] 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.

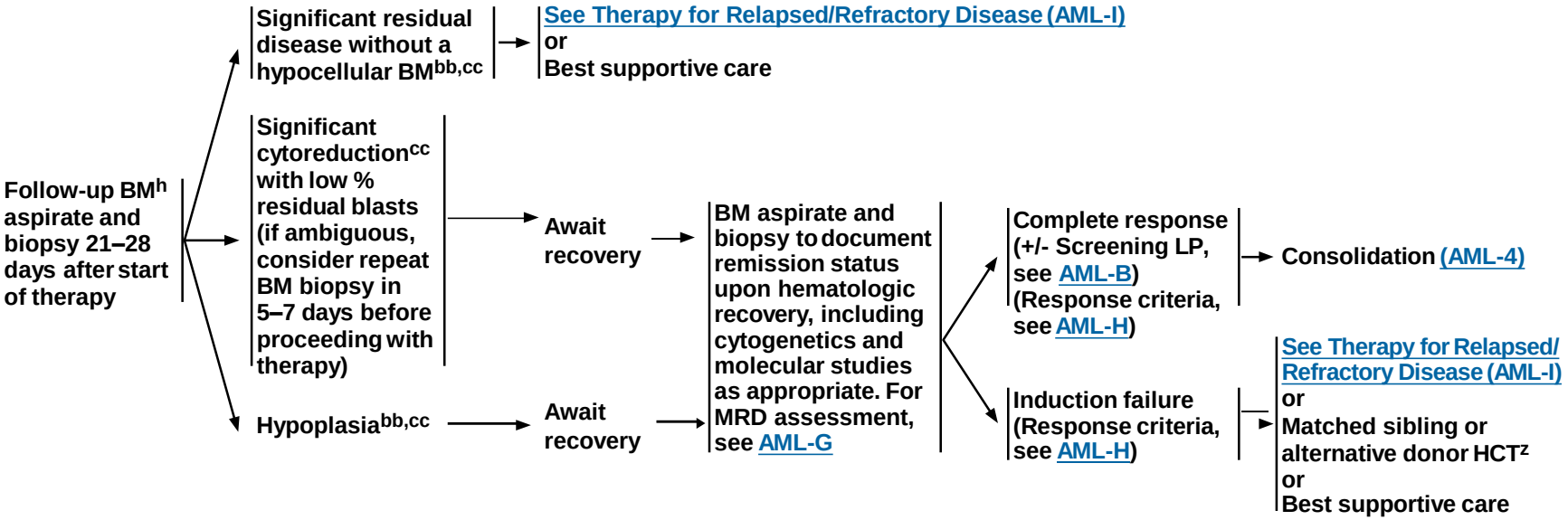
[ff] If daunorubicin 90 mg/m^2 was used in induction, the recommended dose for daunorubicin for reinduction prior to count recovery is 45 mg/m^2 for no more than 2 doses. Analogously, if idarubicin 12 mg/m^2 was used for induction, the early reinduction dose should be limited to 10 mg/m^2 for 1 or 2 doses.

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

Note: All recommendations are category 2A unless otherwise indicated.
Clinical Trials: Participation in clinical trials is encouraged in selected cases.

Acute Myeloid Leukemia

AGE <60 y
AFTER HIGH-DOSE CYTARABINE INDUCTION[i,y,z]



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

[i] 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.

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

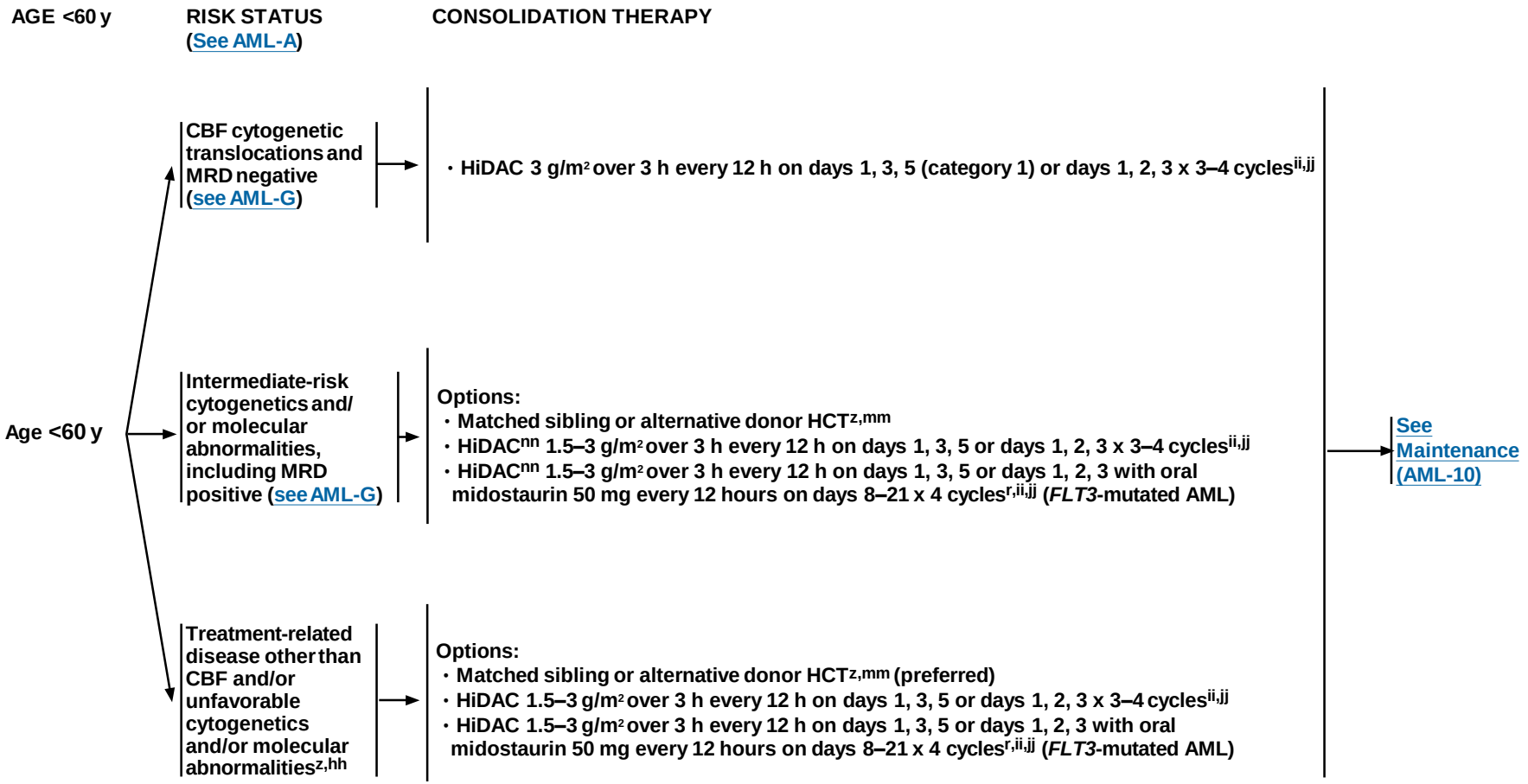
[z] Begin alternate donor search (haploidentical, unrelated donor, or cord blood) if no appropriate matched sibling donor is available and the patient is a candidate for allogeneic HCT. For induction failure, alternative therapy to achieve remission is encouraged prior to HCT.

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

[cc] 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: Participation in clinical trials is encouraged in selected cases.

Acute Myeloid Leukemia



Note: All recommendations are category 2A unless otherwise indicated.
Clinical Trials: Participation in clinical trials is encouraged in selected cases.

Acute Myeloid Leukemia

FOOTNOTES FOR CONSOLIDATION THERAPY (AGE <60 YEARS)

[l] 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.

[r] This regimen is for *FLT3* mutation-positive AML (both ITD and TKD mutations). While midostaurin was not FDAapproved 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] 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.

[hh] *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.

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

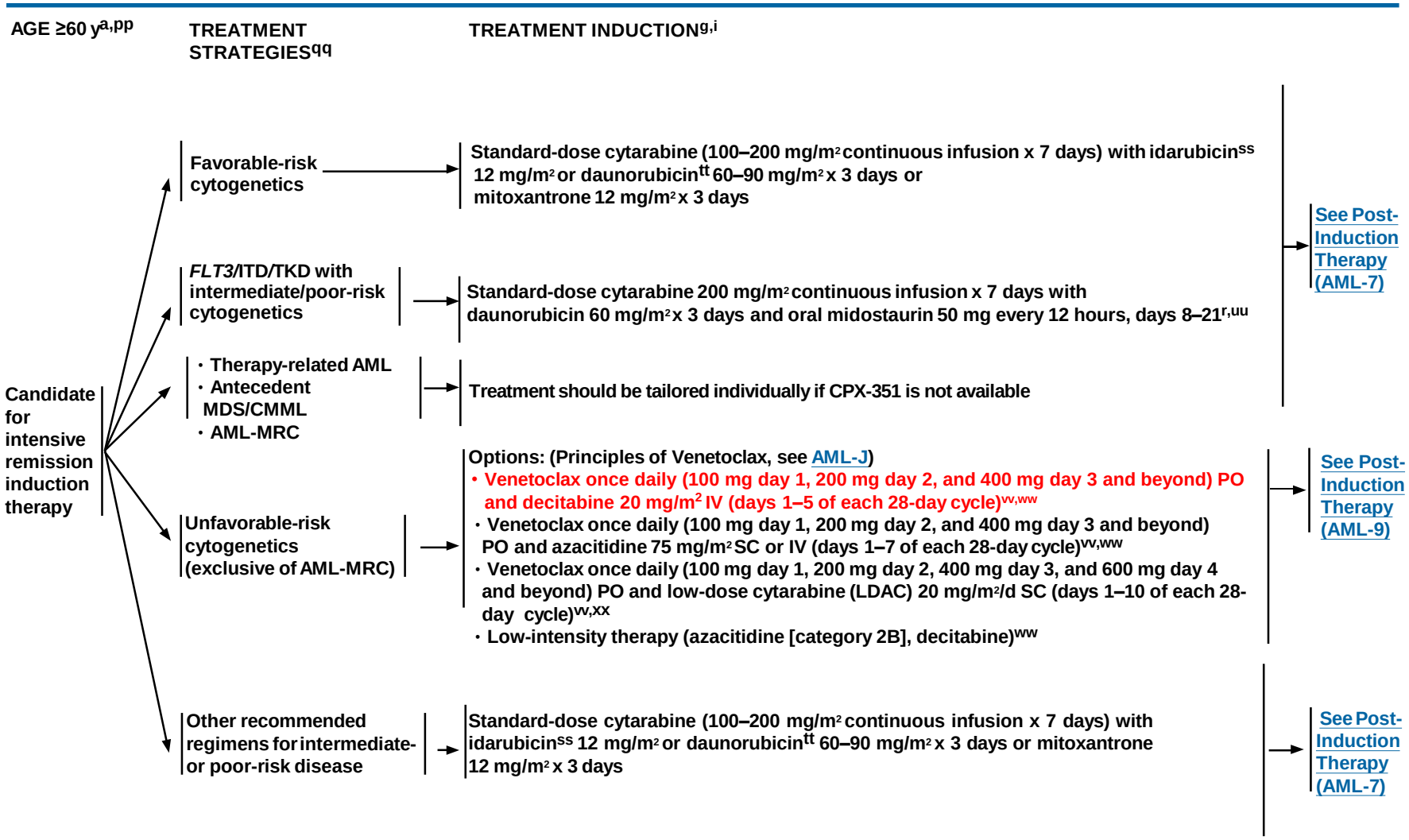
[jj] Alternate dosing of cytarabine for postremission therapy has been reported. Jaramillo S, et al. Blood Cancer J 2017;7:e564.

[mm] 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.

[nn] 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.

Note: All recommendations are category 2A unless otherwise indicated.
Clinical Trials: Participation in clinical trials is encouraged in selected cases.

Acute Myeloid Leukemia



See footnotes on AML-5A

Note: All recommendations are category 2A unless otherwise indicated.
Clinical Trials: Participation in clinical trials is encouraged in selected cases.

Acute Myeloid Leukemia

FOOTNOTES FOR TREATMENT INDUCTION (AGE ≥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.

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

[i] 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.

[l] 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.

[r] This regimen is for *FLT*3 mutation-positive AML (both ITD and TKD mutations). While midostaurin was not FDAapproved 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.

[pp] 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://trmcalculator. fredhutch.org 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.

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

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

[ss] 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]).

[tt] 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). [uu]
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.

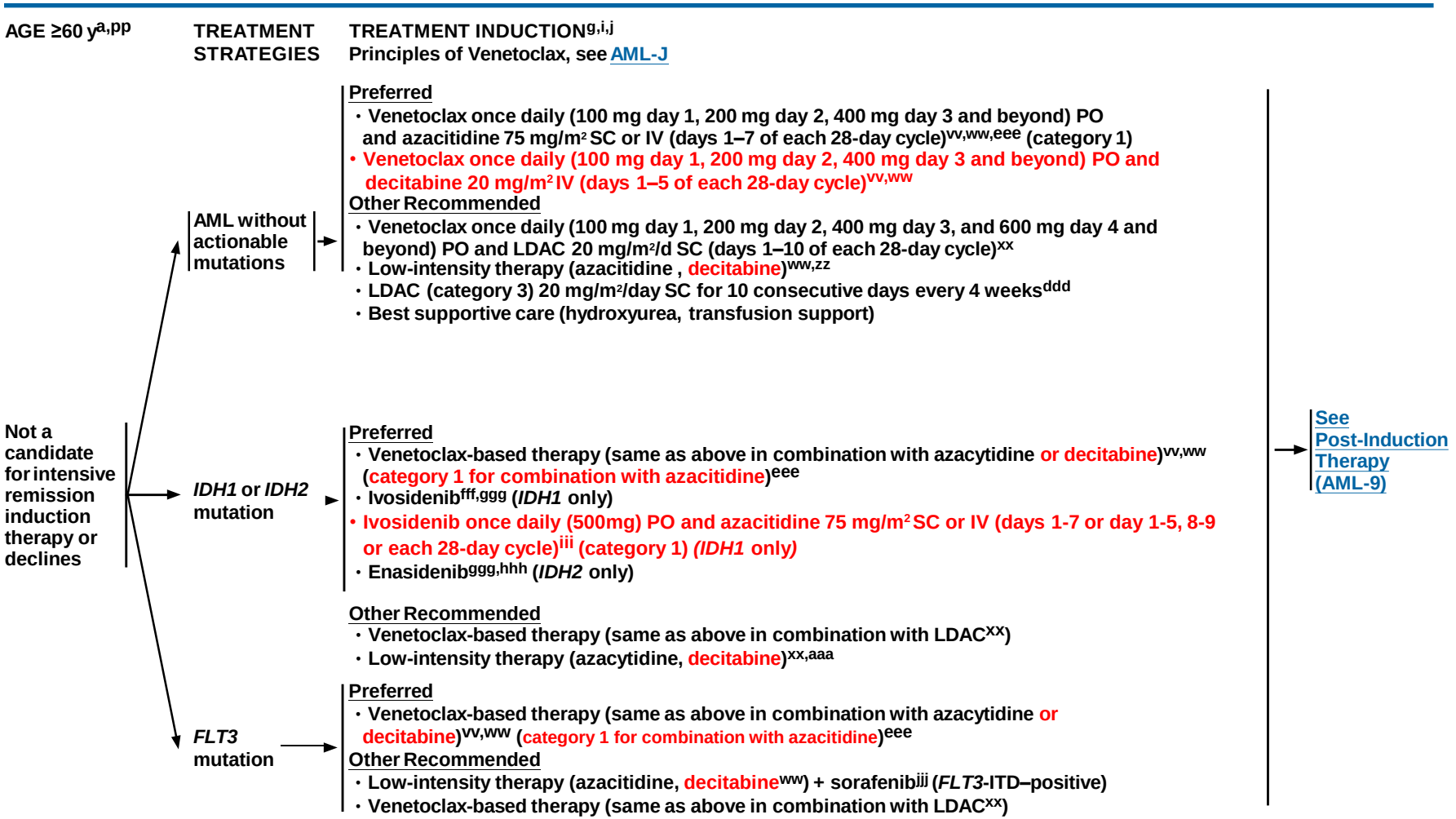
[vv] This regimen may be continued for patients who demonstrate clinical improvement (CR/CRi), with consideration of subsequent transplant, where appropriate. DiNardo CD, et al. Lancet Oncol 2018;19:216-228; Wei A, et al. Blood 2017;130:890; Wei A, et al. Haematologica 2017; Abstract S473; DiNardo CD, Blood 2019;133:7-17; DiNardo CD, et al. N Engl J Med 2020;383:617-629.

[ww] Patients who have progressed to AML from MDS after significant exposure to hypomethylating agents (HMAs) (ie, azacitidine) 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.

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

Note: All recommendations are category 2A unless otherwise indicated.
Clinical Trials: Participation in clinical trials is encouraged in selected cases.

Acute Myeloid Leukemia



See footnotes on AML-6A

Note: All recommendations are category 2A unless otherwise indicated.
Clinical Trials: Participation in clinical trials is encouraged in selected cases.

Acute Myeloid Leukemia

FOOTNOTES FOR TREATMENT INDUCTION (AGE ≥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.

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

[i] 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.

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

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

[pp] 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://trmcalculator.fredhutch.org 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.

[vv] 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.

[ww] Patients who have 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.

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

[zz] 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.

[aaa] 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.

[ddd] Kantarjian HM, et al. J Clin Oncol 2012;30:2670-2677.

[eee] DiNardo CD, et al. N Engl J Med 2020;383:617-629.

[fff] DiNardo CD, et al. Blood 2017;130:725; DiNardo CD, et al. Blood 2017;130:639; Roboz GJ, et al. Blood 2020;135:463-471.

[ggg] When using this agent, 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).

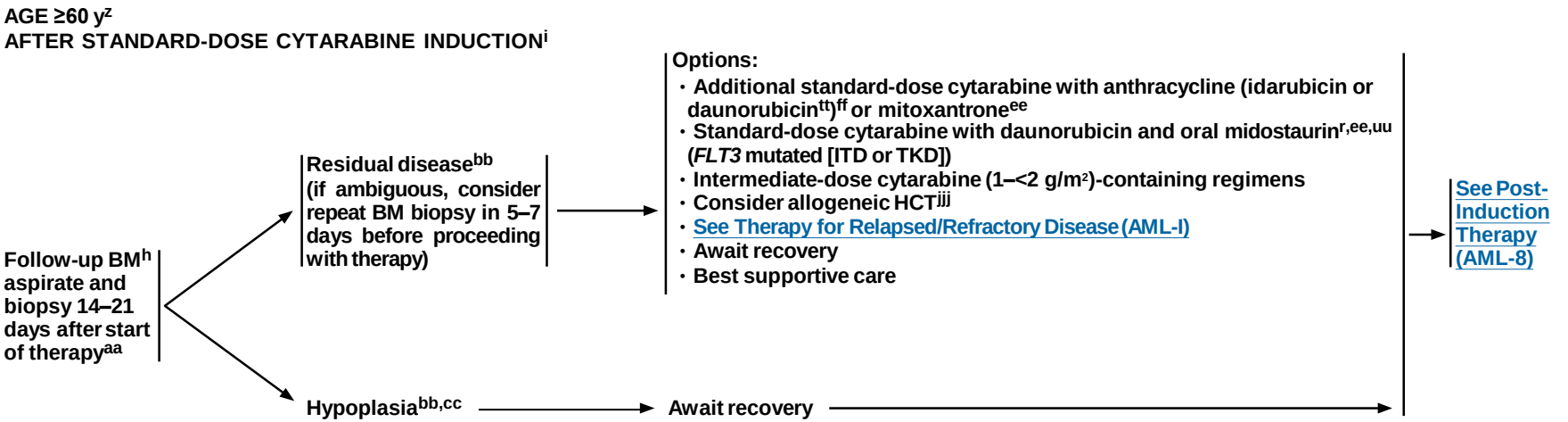
[hhh] Stein EM, et al. Blood 2015;126:323; DiNardo CD, et al. Blood 2017;130:639.

[iii] This regimen is approved for newly-diagnosed AML with an *IDH1* mutation who met at least one of the following criteria: age >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 < 45 mL/min, or other comorbidity. Montesinos P, et al. N Engl J Med 2022;386:1519-153.

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

Note: All recommendations are category 2A unless otherwise indicated.
Clinical Trials: Participation in clinical trials is encouraged in selected cases.

Acute Myeloid Leukemia



h See Monitoring During Therapy (AML-F).

i Consider referral to palliative care 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.

r 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 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.

aa There are limited prospective data to support this recommendation. Othus M, et al. Leukemia 2016;30:1779-1780.

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

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

ee 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 If daunorubicin 90 mg/m² was used in induction, the recommended dose for daunorubicin for reinduction prior to count recovery is 45 mg/m² for no more than 2 doses. Analogously, if idarubicin 12 mg/m² was used for induction, the early reinduction dose should be limited to 10 mg/m² for 1 or 2 doses.

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

tt The complete response rate and 2-year overall survival in patients between 60 and 65 years of age treated with daunorubicin 90 mg/m² are also comparable to the outcome for idarubicin 12 mg/m²; the higher dose daunorubicin did not benefit patients >65 years of age (Löwenberg B, et al. N Engl J Med 2009;361:1235-1248).

uu 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 Allogeneic transplant is a reasonable option in patients who experience failure after re-induction with certain regimens (eg, intermediate- or high-dose cytarabine), and have identified donors available to start conditioning within 4 – 6 weeks from start of induction therapy. Patients without an identified donor would most likely need some additional therapy as a bridge to transplant. HCT may be appropriate for patients with a low level of residual disease post-induction (eg, patients with prior MDS who reverted back to MDS with <10% blasts). It is preferred that this approach be given in the context of a clinical trial. For patients with residual disease after 1 cycle of induction chemotherapy who would not tolerate another intensive salvage, consider a venetoclax-basedregimen.

Note: All recommendations are category 2A unless otherwise indicated.
Clinical Trials: Participation in clinical trials is encouraged in selected cases.

Acute Myeloid Leukemia

AGE ≥60 y
POST-INDUCTION THERAPY

Previous intensive therapy → BM aspirate and biopsy to document remission status upon hematologic recovery (4–6 weeks). For MRD assessment, see AML-G

BM aspirate and biopsy to document remission status upon hematologic recovery (4–6 weeks). For MRD assessment, see AML-G →

- Complete response[lll] (Response criteria, see AML-H) →
  - Able to receive conventional consolidation →
    - Options
      - Allogeneic HCT[mmm]
      - Standard-dose cytarabine (100–200 mg/m²/d x 5–7 d x 1–2 cycles) ± anthracycline (idarubicin or daunorubicin)[ee]
      - Consider intermediate-dose cytarabine 1–1.5 g/m²/d x 4–6 doses x 1–2 cycles for patients with good performance status, normal renal function, and better-risk/normal karyotype with favorable molecular markers
      - Intermediate-dose cytarabine 1–1.5 g/m² over 3 h every 12 h on days 1, 3, and 5 or 1 g/m² over 3 h every 12 h on days 1, 3, and 5 (total 6 doses) for a total of 4 planned cycles with oral midostaurin 50 mg every 12 h on days 8–21[r,nnn]
      - Observation

    → See Maintenance (AML-10)
  - Not able to receive any or all of the recommended consolidation →
    - Maintenance therapy with oral azacitidine 300 mg PO once daily on days 1–14 of each 28-day cycle until progression or unacceptable toxicity (If available) (category 1, preferred)[ooo]
    - Maintenance therapy with hypomethylating regimens every 4–6 weeks until progression[ppp]
      - Azacitidine
      - Decitabine (category 2B)
- Induction failure (Response criteria, see AML-H) →
  - Options
    - Low-intensity therapy (azacitidine)
    - Allogeneic HCT (preferably in clinical trial)
    - See Therapy for Relapsed/Refractory Disease (AML-I)
    - Best supportive care

See footnotes on AML-8A

Note: All recommendations are category 2A unless otherwise indicated.
Clinical Trials: Participation in clinical trials is encouraged in selected cases.

Acute Myeloid Leukemia

FOOTNOTES FOR POST-INDUCTION THERAPY (AGE ≥60 YEARS)

[r] 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.

[ee] 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.

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

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

[nnn] 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.

[ooo] This is not intended to replace consolidation chemotherapy. 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. N Engl J Med 2020;383:2526-2537.

[ppp] Azacitidine: Huls G, et al. Blood 2019;133:1457-1464; Decitabine: Boumber Y, et al. Leukemia 2012;26:2428–3241.

Note: All recommendations are category 2A unless otherwise indicated.
Clinical Trials: Participation in clinical trials is encouraged in selected cases.

Acute Myeloid Leukemia

AGE ≥60 y
POST-INDUCTION THERAPY

Previous lower-intensity therapy → **BM aspirate and biopsy to document remission status upon hematologic recovery (timing is dependent on agent)[qqq] For MRD assessment, see AML-G**

Response (Response criteria, see AML-H) →
Options: (Principles of Venetoclax, see AML-J)
- **Allogeneic HCT[mmm]**
- **Continue on lower-intensity regimen that was previously used per AML-6:**
  - **Hypomethylating regimens (azacitidine, decitiabine) every 4–6 weeks until progression[qq]**
  - **Enasidenib until progression (*IDH2*-mutated AML)[hhh,rrr] or ivosidenib[fff,rrr] (*IDH1*-mutated AML) until progression**
  - **Venetoclax once daily PO and decitabine 20 mg/m² IV (days 1–5 of each 28-day cycle)[qq,rr]**
  - **Venetoclax once daily PO and azacitidine 75 mg/m² SC or IV (days 1–7 of each 28-day cycle)[qq,rr]**
  - **Venetoclax once daily PO and LDAC 20 mg/m²/d SC (days 1–10 of each 28-day cycle)[qq,xx]**
  - **Azacitidine or decitabine + sorafenib (*FLT3*-ITD-mutated AML)[rr,jjj]**

→ **See Maintenance (AML-10)**

No response or progression (Response criteria, see AML-H) → **See Therapy for Relapsed/Refractory Disease (AML-I) or Best supportive care**

[qq] 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. 2017;130:890; Wei A, et al. Haematologica 2017; Abstract S473; DiNardo Roboz GJ, et al. Blood 2020;135:463-471. CD, Blood 2019;133:7-17; DiNardo CD, et al. N Engl J Med 2020;383:617-629.

[rr] Patients who have progressed to AML from MDS after significant exposure to HMAs (ie, azacitidine) 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.

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

[vv] 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). Cortes JE, et al. Blood 2016;128:99-99.

[fff] DiNardo CD, et al. Blood 2017;130:725; DiNardo CD, et al. Blood 2017;130:639; Blood 2017;130:890; Wei A, et al. Haematologica 2017; Abstract S473; DiNardo Roboz GJ, et al. Blood 2020;135:463-471.

[hhh] Stein EM, et al. Blood 2015;126:323; DiNardo CD, et al. Blood 2017;130:639.

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

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

[qqq] Response to treatment with enasidenib or ivosidenib may take 3 – 5 months. 2019;133:7-17.

[rrr] Enasidenib or ivosidenib increases the risk for differentiation syndrome and hyperleukocytosis that may require treatment with hydroxyurea and steroids.

Note: All recommendations are category 2A unless otherwise indicated.
Clinical Trials: Participation in clinical trials is encouraged in selected cases.

Acute Myeloid Leukemia

MAINTENANCE THERAPY

- Patient with intermediate or adverse risk disease:
  - Who received prior intensive chemotherapy and is now in remission
  - Completed no consolidation, some consolidation or a recommended course of consolidation and
  - No allogeneic stem cell transplant is planned

→ Oral azacitidine 300 mg PO daily (if available) on Days 1–14 of each 28-day cycle until progression or unacceptable toxicity[ooo]

Post allogeneic stem cell transplantation, in remission, and history of *FLT3*-ITD → *FLT3* inhibitor maintenance
- Sorafenib[sss, ttt]

Neither of the above scenarios is applicable → Maintenance therapy not recommended

→ See Surveillance (AML-11)

[ooo] This is not intended to replace consolidation chemotherapy. 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. N Engl J Med 2020;383:2526-2537.

[sss] Xuan L, et al. Lancet Oncol 2020;21:1201-1212.

[ttt] Burchert A, et al. J Clin Oncol 2020;38:2993-3002.

Note: All recommendations are category 2A unless otherwise indicated.
Clinical Trials: Participation in clinical trials is encouraged in selected cases.

Acute Myeloid Leukemia

AML SURVEILLANCE AND THERAPY FOR RELAPSED/REFRACTORY DISEASE (AFTER COMPLETION OF CONSOLIDATION)

- 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
- Donor search should be initiated

at first relapse in appropriate patients concomitant with institution of other therapy if no sibling donor has been identified

→ Relapse[uuu] (Response criteria, see AML-H)

→ Comprehensive genomic profiling to determine mutation status of actionable genes

→ Options:
Clinical trial (strongly preferred)
or
Targeted therapy (see AML-I) followed by matched sibling or alternative donor HCT
or
Chemotherapy (see AML-I) followed by matched sibling or alternative donor HCT
or
Repeat initial successful induction regimen[vvv] if ≥12 months since induction regimen
or
Best supportive care

[uuu] Comprehensive molecular profiling (including *IDH1*/*IDH2*, *FLT3* mutations) is suggested as it may assist with selection of therapy and appropriate clinical trials. Molecular testing should be repeated at each relapse or progression.

[vvv] 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 complete response is achieved, then consolidation with allogeneic HCT should be considered.

Note: All recommendations are category 2A unless otherwise indicated.
Clinical Trials: Participation in clinical trials is encouraged in selected cases.

Acute Myeloid Leukemia

RISK STRATIFICATION BY GENETICS IN NON-APL AML[1,2]

Risk Category*	Genetic Abnormality
Favorable	t(8;21)(q22;q22.1); *RUNX1-RUNX1T1* inv(16)(p13.1q22) or t(16;16)(p13.1;q22); *CBFB-MYH11* Biallelic mutated *CEBPA* Mutated *NPM1* without *FLT3*-ITD or with *FLT3*-ITD^{low}†
Intermediate	Mutated *NPM1* and *FLT3*-ITD^{high}† Wild-type *NPM1* without *FLT3*-ITD or with *FLT3*-ITD^{low}† (without adverse-risk genetic lesions) t(9;11)(p21.3;q23.3); *MLLT3-KMT2A*‡ Cytogenetic abnormalities not classified as favorable or adverse
Poor/Adverse	t(6;9)(p23;q34.1); *DEK-NUP214* t(v;11q23.3); *KMT2A* rearranged t(9;22)(q34.1;q11.2); *BCR-ABL1* inv(3)(q21.3q26.2) or t(3;3)(q21.3;q26.2); *GATA2,MECOM(EVI1)* -5 or del(5q); -7; -17/abn(17p) Complex karyotype,§ monosomal karyotype‖ Wild-type *NPM1* and *FLT3*-ITD^{high}† Mutated *RUNX1*¶ Mutated *ASXL1*¶ Mutated *TP53*#

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

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

* Prognostic impact of a marker is treatment-dependent and may change with new therapies.

† Low, low allelic ratio (<0.5); high, high allelic ratio (≥0.5); semiquantitative assessment of *FLT3*-ITD allelic ratio (using DNA fragment analysis) is determined as ratio of the area under the curve "*FLT3*-ITD" divided by area under the curve "*FLT3*-wild type"; regardless of *FLT3* allelic fractions, patients should be considered for HCT, though recent studies indicate that AML with *NPM1* mutation and *FLT3*-ITD low allelic ratio may also have a more favorable prognosis and patients should not routinely be assigned to allogeneic HCT. *FLT3* allelic ratio is not yet pervasively used, and IF not available, the presence of an *FLT3* mutation should be considered high risk unless it occurs concurrently with an *NPM1* mutation, in which case it is intermediate risk. As data emerge, this measure will evolve.

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

§ Three or more unrelated chromosome abnormalities in the absence of 1 of the WHO-designated recurring translocations or inversions, that is, t(8;21), inv(16) or t(16;16), t(9;11), t(v;11)(v;q23.3), t(6;9), inv(3) or t(3;3); AML with *BCR-ABL1*.

‖ Defined by the presence of 1 single monosomy (excluding loss of X or Y) in association with at least 1 additional monosomy or structural chromosome abnormality (excluding CBF AML).

¶ These markers should not be used as an adverse prognostic marker if they co-occur with favorable-risk AML subtypes.

TP53 mutations are significantly associated with AML with complex and monosomal karyotype.

Note: All recommendations are category 2A unless otherwise indicated.
Clinical Trials: Participation in clinical trials is encouraged in selected cases.

Continued

Acute Myeloid Leukemia

RISK STRATIFICATION BY GENETICS IN NON-APL AML[1]

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

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

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

‡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 basic leucine zipper (bZIP) region of CEBPA, irrespective 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 adverserisk 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 core-binding factor 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.

[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.

Note: All recommendations are category 2A unless otherwise indicated.
Clinical Trials: Participation in clinical trials is encouraged in selected cases.

Continued

Acute Myeloid Leukemia

FAMILIAL GENETIC ALTERATIONS IN AML

- 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
  - 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.

Note: All recommendations are category 2A unless otherwise indicated.
Clinical Trials: Participation in clinical trials is encouraged in selected cases.

Acute Myeloid Leukemia

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 AML T-cell ALL	Thrombocytopenia Platelet dysfunction		Exon sequencing and gene rearrangement testing for *RUNX1*
Thrombocytopenia 2 (OMIM 188000)	*ANKRD26*	Autosomal dominant	MDS AML	Thrombocytopenia 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 AML 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 AML CMML B-ALL Myeloma	Thrombocytopenia Platelet dysfunction		Exon sequencing and gene rearrangement testing for *ETV6*
Familial MDS/AML with mutated *GATA2* (OMIM 137295)	*GATA2*	Autosomal dominant	MDS AML CMML	Monocytopenia Lymphopenia (NK cell, dendritic cell, B-cell, or CD4+ T-cell)	Sensorineural deafness Immunodeficiency Cutaneous warts Pulmonary alveolar proteinosis MonoMAC syndrome Emberger syndrome	Exon sequencing, intron 5 enhancer region sequencing, and gene rearrangement testing for *GATA2*

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Continued

Note: All recommendations are category 2A unless otherwise indicated.
Clinical Trials: Participation in clinical trials is encouraged in selected cases.

Acute Myeloid Leukemia

FAMILIAL GENETIC ALTERATIONS IN AML

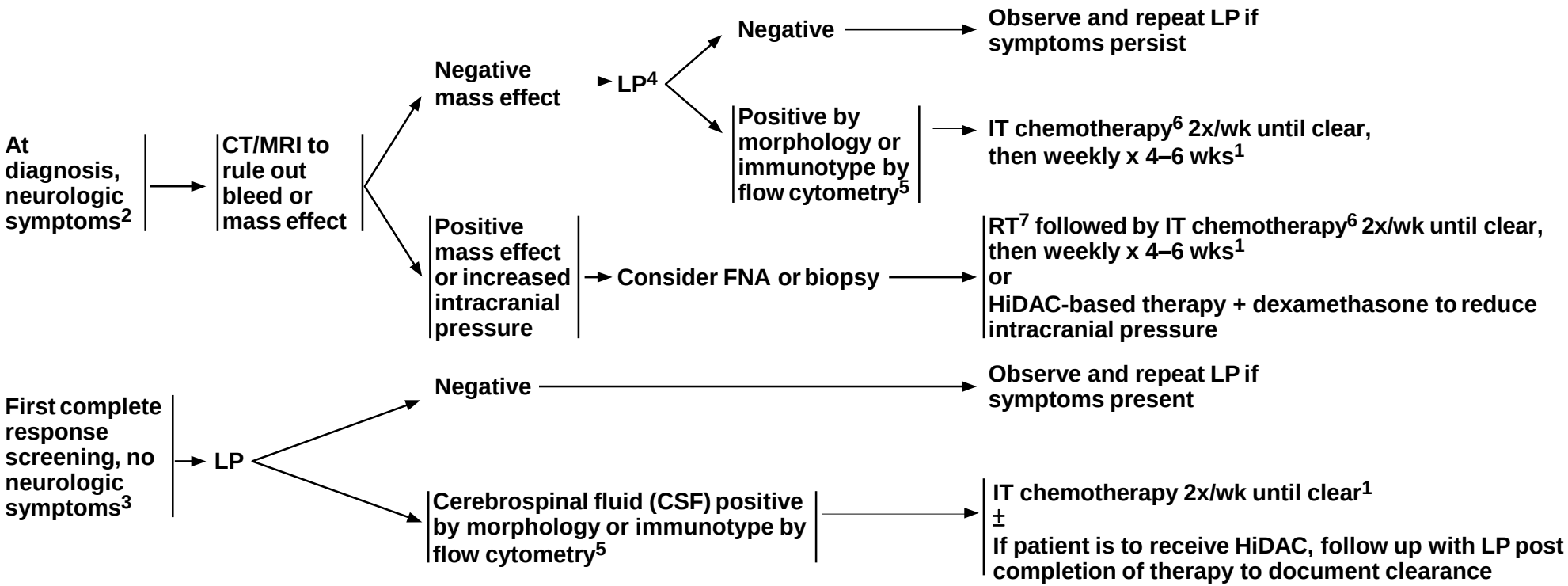
Name of Syndrome	Causative Gene(s)	Pattern of Inheritance	Characteristic Malignancy	Other Hematopoietic Abnormalities	Other Associated Conditions	Recommended Diagnostic Test
Familial AML with mutated *MBD4*	*MBD4*	Autosomal dominant	AML		Colonic polyps	Exon sequencing and gene rearrangement testing for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

Adapted with permission from: Churpek JE, Godley LA. Familial acute leukemia and myelodysplastic syndromes. In: UpToDate, Post TW (Ed), UpToDate, Waltham, MA. (January 31, 2020) Copyright © 2020 UpToDate, Inc. For more information visit www.uptodate.com.

Note: All recommendations are category 2A unless otherwise indicated.
Clinical Trials: Participation in clinical trials is encouraged in selected cases.

Acute Myeloid Leukemia

EVALUATION AND TREATMENT OF CNS LEUKEMIA[1]



1 Further CNS prophylaxis per institutional practice.

2 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.

3 Screening LP should be considered at first remission before first consolidation for patients with monocytic differentiation, mixed phenotype acute leukemia (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.

4 In the presence of circulating blasts, administer IT chemotherapy with diagnostic LP.

5 If equivocal, consider repeating LP with morphology or immunotype by flow cytometry to delineate involvement.

6 Induction chemotherapy should be started concurrently. However, for patients receiving high-dose cytarabine, 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.

7 Concurrent use of CNS RT with high-dose cytarabine or IT methotrexate may increase risk of neurotoxicity. See Principles of Radiation Therapy (AML-C).

Note: All recommendations are category 2A unless otherwise indicated.
Clinical Trials: Participation in clinical trials is encouraged in selected cases.

Acute Myeloid Leukemia

PRINCIPLES OF RADIATION THERAPY

General Principles

- **Patients who present with isolated extramedullary disease (myeloid sarcoma) should be treated with systemic therapy. Local therapy (radiation 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[1] followed by IT chemotherapy[2] 2x/wk until clear, then weekly x 4–6 weeks[3]**

1 Concurrent use of CNS RT with high-dose cytarabine or IT methotrexate may increase risk of neurotoxicity.
2 Induction chemotherapy should be started concurrently. However, for patients receiving high-dose cytarabine, 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.
3 Further CNS prophylaxis per attending physician practice.

Note: All recommendations are category 2A unless otherwise indicated.
Clinical Trials: Participation in clinical trials is encouraged in selected cases.

Acute Myeloid Leukemia

GENERAL CONSIDERATIONS AND SUPPORTIVE CARE FOR AML PATIENTS 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 could 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 females; proton pump inhibitor, aggressive antiemetic prophylaxis, and stool softeners to reduce risk of 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. 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 transplant.

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 [published online ahead of print, Jun 29].

Note: All recommendations are category 2A unless otherwise indicated.
Clinical Trials: Participation in clinical trials is encouraged in selected cases.

Acute Myeloid Leukemia

PRINCIPLES OF SUPPORTIVE CARE FOR AML

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

General

- **Blood products:**
  - **Leukocyte-depleted products used for transfusion.**
  - **All AML patients are at risk for acute graft-versus-host disease (aGVHD) and management should be based on institutional practice/ preference.**
  - **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.[1]**
  - **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. The patient should not be rechallenged with HiDAC in future treatment cycles.[2]**
- **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.[3] Outcomes with other azoles, such as voriconazole, echinocandins, or amphotericin B, may produce equivalent results.**

1 Patients who are alloimmunized should receive cross-match – compatible and/or HLA-specific blood products.

2 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.

3 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.

Note: All recommendations are category 2A unless otherwise indicated.
Clinical Trials: Participation in clinical trials is encouraged in selected cases.

Acute Myeloid Leukemia

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 PO_4, 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 there is failure to recover counts within 5 weeks.
- Patients 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.

Note: All recommendations are category 2A unless otherwise indicated.
Clinical Trials: Participation in clinical trials is encouraged in selected cases.

Acute Myeloid Leukemia

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 patient 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 who 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 polymerase chain reaction (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.
  - For favorable-risk patients, if MRD is persistently positive after induction and/or consolidation, consider a clinical trial or alternative therapies, including allogeneic transplantation.
  - 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 transplantation.[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.

Note: All recommendations are category 2A unless otherwise indicated.
Clinical Trials: Participation in clinical trials is encouraged in selected cases.

Acute Myeloid Leukemia

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**
  - **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 – patient independent of transfusions**
  - **Absolute neutrophil count >1000/mcL (blasts <5%)**
  - **Platelets ≥100,000/mcL (blasts <5%)**
    - **CR without MRD (CR_{MRD-})[2]**
      - **If studied pretreatment, CR with negativity for a genetic marker by RT-PCR or CR with negativity by MFC**
      - **Sensitivity varies by marker and method used; analyses should be done in experienced laboratories.**
      - **Molecular CR – molecular studies negative**
- **CRh - partial hematologic recovery, defined as <5% blasts in the BM, no evidence of disease (NED), and partial recovery of peripheral blood counts (platelets >50 x 10^9/L and ANC >0.5 x 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[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.**
- **Induction failure – Failure 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 failure 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, et al. 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.

Note: All recommendations are category 2A unless otherwise indicated.
Clinical Trials: Participation in clinical trials is encouraged in selected cases.

Acute Myeloid Leukemia

THERAPY FOR RELAPSED/REFRACTORY DISEASE[1]

Clinical trial[1]

Targeted therapy:

- Therapy for AML with *FLT3*-ITD mutation
  - Gilteritinib[2] (category 1)
  - Hypomethylating agents (HMAs) (azacytidine or decitabine) + sorafenib[3,4]
- Therapy for AML with *FLT3*-TKD mutation
  - Gilteritinib[2] (category 1)
- Therapy for AML with *IDH2* mutation
  - Enasidenib, if available[5]
- Therapy for AML with *IDH1* mutation
  - Ivosidenib, if available [6]

Aggressive therapy for appropriate patients:

- Cladribine + cytarabine + G-CSF[8] ± mitoxantrone or idarubicin[9,10]
- HiDAC (if not received previously in treatment) ± (idarubicin or daunorubicin or mitoxantrone)[11]
- Fludarabine + cytarabine + G-CSF[8] ± idarubicin[12,13]
- Etoposide + cytarabine ± mitoxantrone[14]
- Clofarabine ± cytarabine ± idarubicin[15,16]

Less aggressive therapy:

- HMAs (azacytidine or decitabine)
- LDAC (category 2B)
- Venetoclax[17] + HMA/LDAC[18,19]

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

2 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.

3 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.

4 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.

5 Stein EM, DiNardo CD, Pollyea DA, et al. Enasidenib in mutant *IDH2* relapsed orrefractory acute myeloid leukemia. Blood 2017;130:722-731.

6 DiNardo CD, Stein EM, de Botton S, et al. Durable remissions with ivosidenib inIDH1- mutated relapsed or refractory AML. N Eng JMed 2018;378:2386-2398.

8 An FDA-approved biosimilar is an appropriate substitute for filgrastim.

9 Robak T, Wrzesień-Kuś A, Lech-Maranda E, et al. Combination regimen ofcladribine (2-chlorodeoxyadenosine), cytarabine and G-CSF (CLAG) as induction therapy for patients with relapsed or refractory acute myeloid leukemia. Leuk Lymphoma2000;39:121-129.

10 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.

11 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.

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

13 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.

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

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

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

17 See Principles of Venetoclax Use With HMA in AML Patients (AML-J).

18 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.

19 DiNardo CD, Rausch CR, Benton C, et al. Clinical experience with the BCL2-inhibitor venetoclax in combination therapy for relapsed and refractory acute myeloid leukemiaand related myeloid malignancies. Am J Hematol 2018;93:401-407.

Note: All recommendations are category 2A unless otherwise indicated.
Clinical Trials: Participation in clinical trials is encouraged in selected cases.

Taipei Veterans General Hospital
Practice Guidelines Oncology

Acute Lymphoid Leukemia

Diagnosis

Acute lymphoblastic leukemia (ALL)[a,b,c] →

DIAGNOSIS

The diagnosis of ALL generally requires demonstration of ≥20% bone marrow lymphoblasts[d] upon hematopathology review of bone marrow aspirate and biopsy materials, which includes:

- Morphologic assessment of Wright-Giemsa stained bone marrow aspirate smears, and H&E stained core biopsy and clot sections
- Comprehensive flow cytometric immunophenotyping[e]

GENETIC CHARACTERIZATION

Optimal risk stratification and treatment planning requires testing marrow or peripheral blood lymphoblasts for specific recurrent genetic abnormalities using:

- Karyotyping of G-banded metaphase chromosomes (cytogenetics)
- Reverse transcriptase-polymerase chain reaction (RT-PCR) testing for fusion genes (eg, *BCR-ABL*). Other fusions that describe Ph-like ALL[f]
- **Comprehensive testing by next-generation sequencing (NGS) for gene fusions and pathogenic mutations is recommended.[g]**

CLASSIFICATION

Together, these studies allow determination of the World Health Organization (WHO) ALL subtype[a] and cytogenetic risk group[g]

→ See Workup and Risk Stratification (ALL-2)

[a]Subtypes: B-cell lymphoblastic leukemia/lymphoma with recurrent genetic abnormalities include hyperdiploidy, hypodiploidy, and commonly occurring translocations: t(9;22)(q34;q11.2)[*BCR-ABL1*]; t(v;11q23)[MLL rearranged]; t(12;21)(p13;q22)[ETV6-RUNX1]; t(1;19)(q23;p13.3)[TCF3-PBX1]; t(5;14)(q31;q32)[IL3-IGH;relatively rare]. B-cell lymphoblastic leukemia/lymphoma, not otherwise specified. T-cell lymphoblastic leukemia/lymphoma.

[b]Criteria for classification of mixed phenotype acute leukemia (MPAL) should be based on the WHO 2008 criteria. Note that in ALL, myeloid-associated antigens such as CD13 and CD33 may be expressed, and the presence of these myeloid markers does not exclude the diagnosis of ALL.

[c]Treatment of Burkitt leukemia/lymphoma – see NCCN Guidelines for Non-Hodgkin's Lymphomas.

[d]While these guidelines pertain primarily to patients with leukemia, patients with lymphoblastic lymphoma (LL) (B- or T-cell) would likely also benefit from ALL-like regimens. There are limited data available regarding treatment options and patients should be treated in a center that has experience with LL. See Discussion.

[e]See Typical Immunophenotype by Major ALL Subtypes (ALL-A).

[f]For more information regarding Ph-like ALL, please see the Discussion.

g The Ph-like phenotype is associated with recurrent gene fusions and mutations that activate tyrosine kinase pathways and includes gene fusions involving *ABL1, ABL2, CRLF2, CSF1R, EPOR, JAK2*, or *PDGFRB* and mutations involving *FLT3, IL7R, SH2B3, JAK1, JAK3*, and *JAK2* (in combination with *CRLF2* gene fusions). Testing for these abnormalities at diagnosis may aid in risk stratification. The safety and efficacy of targeted agents in this population is an area of active research. For more information regarding Ph-like ALL, please see the Discussion. In cases of hypodiploid ALL where germline TP53 mutations are common, testing should be considered.

CYTOGENETIC RISK GROUPS FOR B-ALL

RISK GROUPS	CYTOGENETICS
Good risk	• Hyperdiploidy (51–65 chromosomes) ▸ Cases with trisomy of chromosomes 4, 10, and 17 appear to have the most favorable outcome • t(12;21)(p13;q22): *ETV6-RUNX1*[a]
Poor risk	• Hypodiploidy[b,c] (<44 chromosomes) • *KMT2A* rearranged (t[4;11] or others) • t(v;14q32)/IgH • t(9;22)(q34;q11.2): *BCR-ABL1* (defined as high risk in the pre-TKI era) • Complex karyotype (5 or more chromosomal abnormalities) • *BCR-ABL1*-like (Ph-like) ALL ▸ JAK-STAT (*CRLF2r*,[c,d] *EPORr*, *JAK1/2/3r*, *TYK2r*, mutations of *SH2B3*, *IL7R*, *JAK1/2/3*) ▸ ABL class (rearrangements of *ABL1*, *ABL2*, *PDGFRA*, *PDGFRB*, *FGFR*) ▸ Other (*NTRKr*, *FLT3r*, *LYNr*, *PTK2Br*) • Intrachromosomal amplification of chromosome 21 (iAMP21) • t(17;19): *TCF3-HLF* fusion • Alterations of *IKZF1*[e,f]

[a] The translocation t(12;21)(p13;q22) is typically cryptic by karyotyping and requires FISH or PCR to identify.
[b] There are other results that are not less than 44 chromosomes that may be equivalent to hypodiploidy and have the same implications. It is important to distinguish true hypodiploidy from masked hypodiploidy, which results from the doubling of hypodiploid clones. Carroll AJ, Shago M, Mikhail FM, et al. Masked hypodiploidy: Hypodiploid acute lymphoblastic leukemia (ALL) mimicking hyperdiploid ALL in children: A report from the Children's Oncology Group. Cancer Genet 2019;238:62-68.
[c] Alternatively defined as DNA index less than protocol-defined threshold or other clear evidence of hypodiploid clone. Hypodiploid ALL is also often associated with *TP53* loss of function mutations and Li-Fraumeni syndrome.
[d] Jain N, Roberts KG, Jabbour E, et al. Ph-like acute lymphoblastic leukemia: a high-risk subtype in adults. Blood 2017;129:572-581; Roberts KG, Li Y, Payne-Turner D, et al. Targetable kinase-activation lesions in Ph-like acute lymphoblastic leukemia. N Engl J Med 2014;371:1005-1015.
[e] Mullighan CG, Su X, Zhang J, et al. Deletion of IKZF1 and prognosis in acute lymphoblastic leukemia. N Engl J Med 2009;360:470-480; Stanulla M, Dagdan E, Zaliova M, et al. IKZF1plus defines a new minimal residual disease-dependent very-poor prognostic profile in pediatric B-cell precursor acute lymphoblastic leukemia. J Clin Oncol 2018;36:1240-1249.
[f] Emerging evidence suggests *DUX4*r ALL is favorable. Additionally in cases of *DUX4*r, *IKZF1* alterations do not confer poor prognosis.

Workup

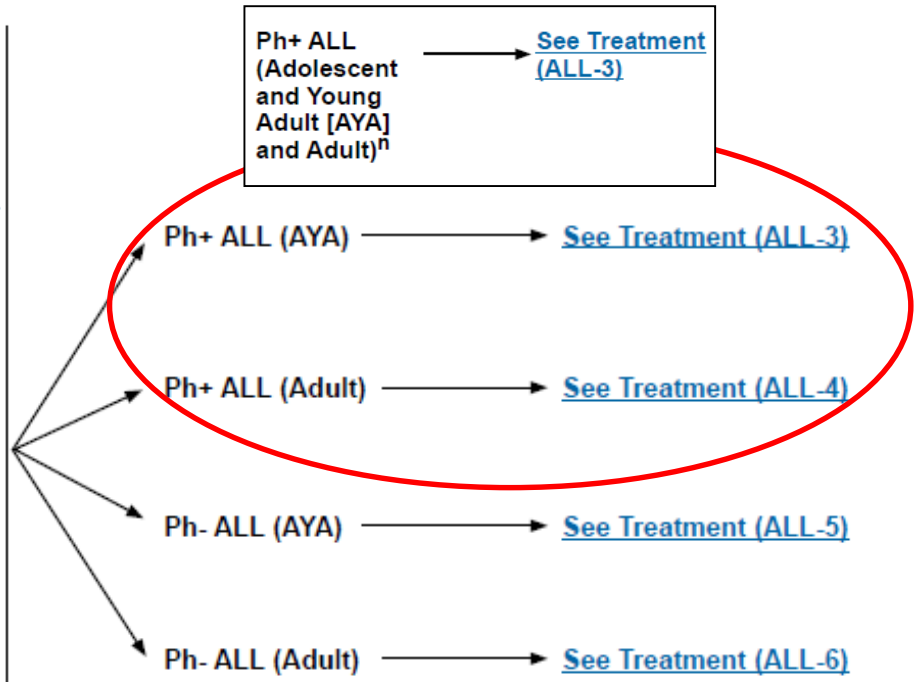
1. CT of neck/chest/abdomen/pelvis with IV contrast, as indicated for symptoms.
2. Consider PET/CT if lymphomatous involvement is suspected and/or confirmed by CT imaging

- For patients with possible cancer predisposition syndromes, principles of cancer risk assessment and counseling should be taken into consideration

WORKUP[h]

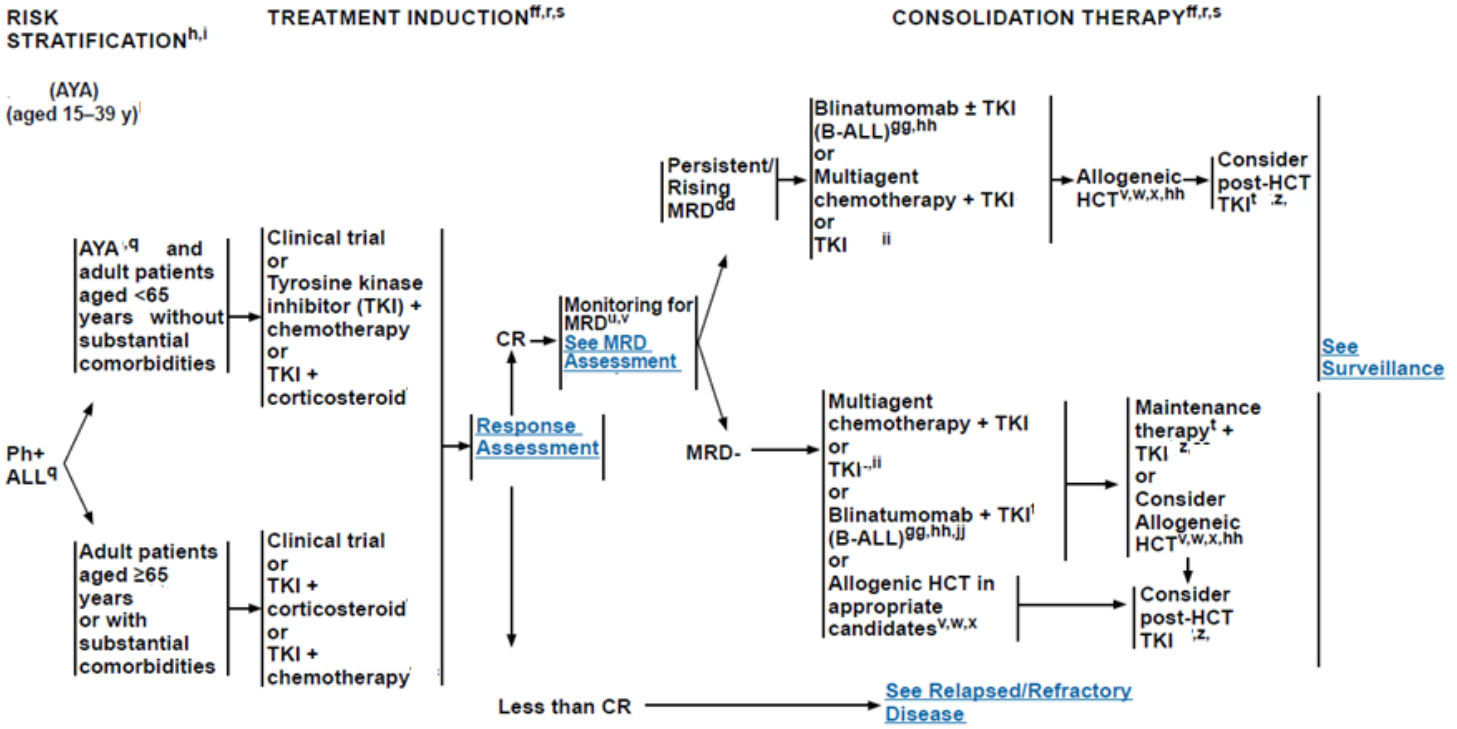
- History and physical (H&P)
- Complete blood count (CBC), platelets, differential, chemistry profile
- Disseminated intravascular coagulation (DIC) panel: d-dimer, fibrinogen, prothrombin time (PT), partial thromboplastin time (PTT)
- Tumor lysis syndrome (TLS) panel: lactate dehydrogenase (LDH), uric acid, K, Ca, Phos (See Tumor Lysis Syndrome in the NCCN Guidelines for Non-Hodgkin's Lymphomas)
- CT/MRI of head, if neurologic symptoms[i]
- Lumbar puncture (LP)[i,j]
  - See Evaluation and Treatment of Extramedullary Involvement (ALL-C)
  - Consider intrathecal (IT) chemotherapy
- CT of chest (for patients with T-cell ALL [T-ALL])
- Testicular exam
- Infection evaluation:
  - Screen for active infections if febrile or for symptomatic opportunistic infections
  - Initiate empirical treatment, as appropriate (See NCCN Guidelines for Prevention and Treatment of Cancer-Related Infections)
- Echocardiogram or cardiac scan should be considered in all patients, since anthracyclines are important components of ALL therapy, but especially in patients with prior cardiac history and prior anthracycline exposure of clinical symptoms suggestive of cardiac dysfunction.
- Central venous access device of choice
- Human leukocyte antigen (HLA) typing (except for patients with a major contraindication to hematopoietic cell transplant [HCT])
- In patients with poor-risk features who lack a sibling donor, consider early evaluation and search for an alternative donor

RISK STRATIFICATION



[h]The following list represents minimal recommendations; other testing may be warranted according to clinical symptoms and discretion of the clinician.
[i]For patients with major neurologic signs or symptoms at diagnosis, appropriate imaging studies should be performed to detect meningeal disease, chloromas, or central nervous system (CNS) bleeding. See Evaluation and Treatment of Extramedullary Involvement (ALL-C).
[j]Timing of LP should be consistent with the chosen treatment regimen. Pediatric-inspired regimens typically include LP at the time of diagnostic workup. The panel recommends that LP, if performed, be done concurrently with initial IT therapy.
[n]The ALL Panel considers AYA to be within the age range of 15–39 years. However, this age range is not a firm reference point because some of the recommended regimens have not been comprehensively tested across all ages.

Ph+ ALL (Adolescent and Young Adult [AYA] and Adult)



[q] It is reasonable to approach the initial treatment of blast phase CML with similar strategies to Ph+ ALL, with a goal of proceeding to hematopoietic cell transplantation (HCT).

[r] ALL treatment regimens include CNS prophylaxis. This may be particularly important when using agents without known CNS penetrance including blinatumomab and certain TKIs.

[v] Optimal timing of HCT is not clear. For fit patients, additional therapy is recommended to eliminate MRD prior to transplant. Proceeding to allogeneic HCT with MRD is not optimal.

[w] Data suggest that for younger patients (aged ≤21 years), particularly for those who achieve MRD negativity, allogeneic HCT may not offer an advantage over chemotherapy + TKI. Schultz KR, et al. J Clin Oncol 2009;27:5175-5181; Schultz KR, et al. Leukemia 2014;28:1467-1471.

[x] Many variables determine eligibility for allogeneic HCT including donor availability, depth of remission, comorbidities, and social support.

[z] The recommended duration of TKI after HCT is at least 1 year. The recommended duration of TKI during maintenance chemotherapy is at least until completion of maintenance chemotherapy. The optimal duration of TKI is unknown in both settings.

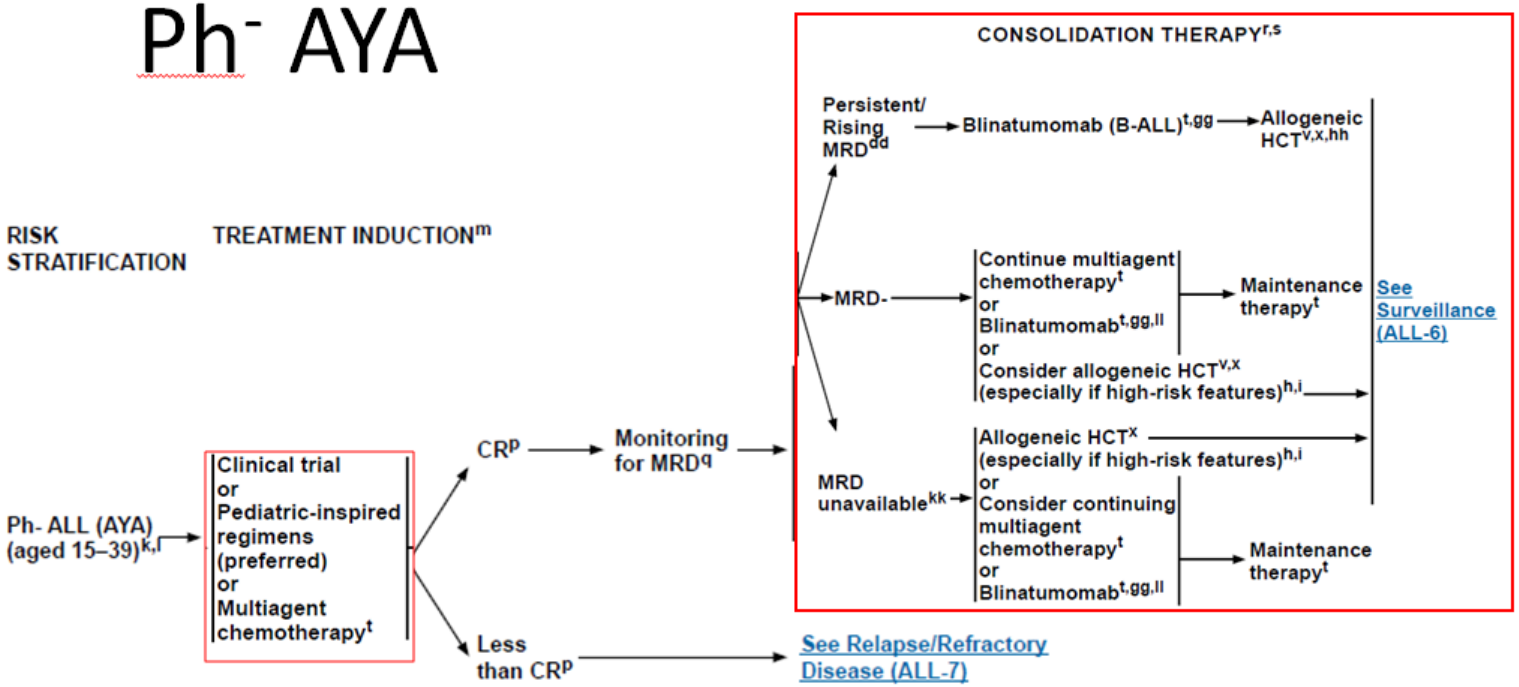
[ff] TKI options include (in alphabetical order): bosutinib, dasatinib, imatinib, nilotinib, or ponatinib. Not all TKIs have been directly studied within the context of each specific regimen and the panel notes that there are limited data for bosutinib in Ph+ ALL. Use of a specific TKI should account for anticipated/prior TKI intolerance, *BCR-ABL1* mutations, and disease-related features. For contraindicated mutations,

[hh] Although long-term remission after blinatumomab treatment is possible, allogeneic HCT should be considered as consolidative therapy.

[ii] TKI monotherapy is seldom effective as induction, however it may be considered as consolidation/maintenance in those unfit for additional therapies.

[jj] For patients who are not candidates for multi-agent chemotherapy.

Ph- AYA



[g]Cytogenetic risk groups are defined as follows:
Good risk: Hyperdiploidy (51–65 chromosomes and/or DNA index >1.16; cases with trisomy of chromosomes 4, 10, and 17 appear to have the most favorable outcome); t(12;21)(p13;q22): ETV6-RUNX1;
Poor risk: Hypodiploidy (<44 chromosomes and/or DNA index <0.81); t(v;11q23): MLL rearranged; t(9;22)(q34;q11.2): *BCR-ABL* (defined as high risk in the pre-TKI era); Complex karyotype (5 or more chromosomal abnormalities).

[h]Chronological age is a poor surrogate for fitness for therapy. Patients should be evaluated on an individual basis, including for the following factors: end-organ reserve, end-organ dysfunction, and performance status.

[l]For additional considerations in the management of AYA patients with ALL, see the NCCN Guidelines for Adolescent and Young Adult Oncology.

[m]All ALL treatment regimens include CNS prophylaxis.

[n]See Principles of Chemotherapy (ALL-D).

[p]See Response Criteria (ALL-E).

[q]See Minimal Residual Disease Assessment (ALL-F).

[v]See Principles of Chemotherapy (ALL-D). All regimens include induction/delayed intensification (especially for pediatric-inspired regimens) and maintenance therapy.

[w]High WBC count (≥30 x 10^9/L for B lineage or ≥100 x 10^9/L for T lineage) is considered a high-risk factor based on some studies in ALL. Data demonstrating the effect of WBC counts on prognosis are less firmly established for adults than for the pediatric population.

[t] See Principles of Systemic Therapy

[dd] The prognostic significance of MRD positivity may be regimen-, ALL subtype-, and/or ALL risk-dependent. MRD timepoints and levels prompting allogeneic HCT should be guided by the specific treatment protocol being used. In general, MRD positivity at the end of induction predicts high relapse rates and should prompt evaluation for allogeneic HCT. Therapy aimed at eliminating MRD prior to allogeneic HCT is preferred when possible (See Discussion).

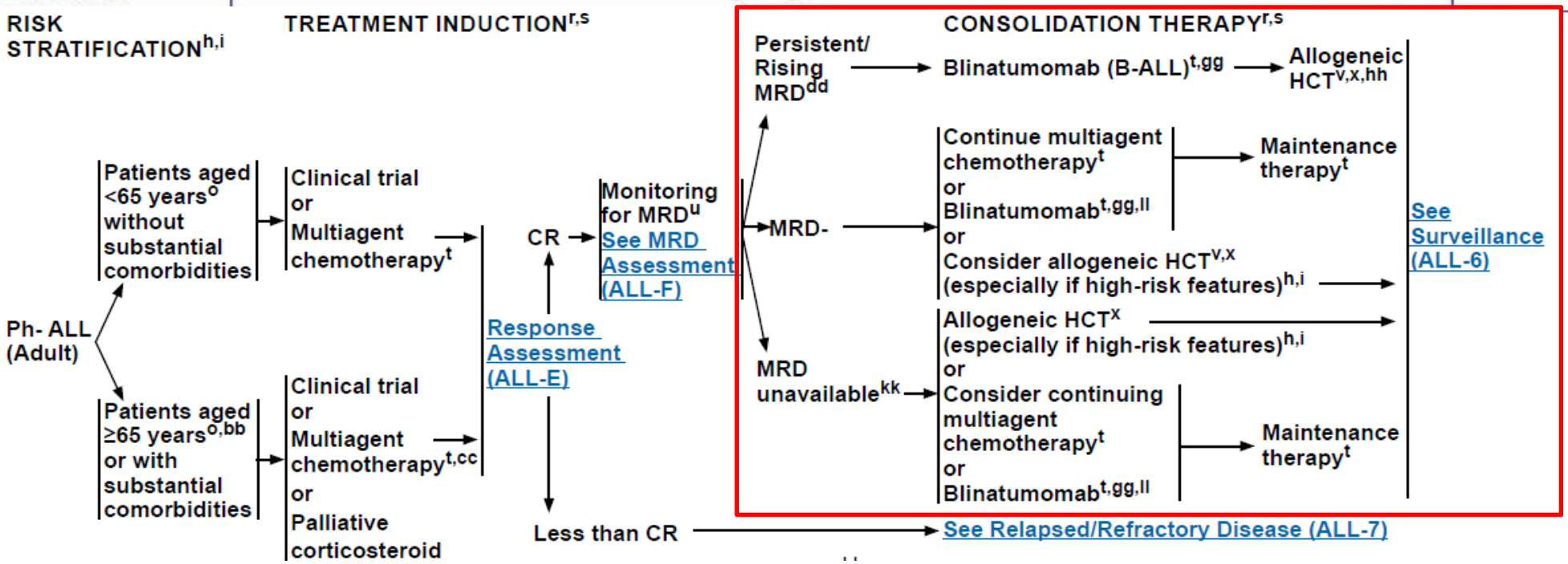
[gg] See Supportive Care: Toxicity Management (ALL-C 2 of 4).

[hh] Although long-term remission after blinatumomab treatment is possible, allogeneic HCT should be considered as consolidative therapy.

[kk] Consider retesting for MRD at first available opportunity.

[ll] Blinatumomab can be considered for consolidation in patients induced with inotuzumab ozogamicin + mini-hyperCVD, or in patients for whom multiagent chemotherapy is contraindicated.

Ph- Adults



[h] See Cytogenetic Risk Groups for B-ALL (ALL-A).

[i] High WBC count (≥30 x 10^9/L for B lineage or ≥100 x 10^9/L for T lineage) is considered a high-risk factor based on some studies in ALL. Data demonstrating the effect of WBC counts on prognosis are less firmly established for adults than for the pediatric population and likely superseded by MRD quantification after treatment.

[o] Chronological age is a poor surrogate for fitness for therapy. Patients should be evaluated on an individual basis, including for the following factors: end-organ reserve, end-organ dysfunction, and performance status.

[r] ALL treatment regimens include CNS prophylaxis. This may be particularly important when using agents without known CNS penetrance including blinatumomab and certain TKIs. See Evaluation and Treatment of Extramedullary Involvement (ALL-B).

[s] See Principles of Supportive Care (ALL-C).

[t] See Principles of Systemic Therapy (ALL-D).

[u] See Minimal/Measurable Residual Disease Assessment (ALL-F).

[v] Optimal timing of HCT is not clear. For fit patients, additional therapy is recommended to eliminate MRD prior to transplant. Proceeding to allogeneic HCT with MRD is not optimal.

[x] Many variables determine eligibility for allogeneic HCT including donor availabiltiy, depth of remission, comorbidities, and social support.

[bb] For additional considerations in the management of adult patients 65 years and over with ALL, see the NCCN Guidelines for Older Adult Oncology.

[cc] Consider dose modifications appropriate for patient age and performance status. See Principles of Systemic Therapy - Treatment of Adults ≥65 years or Adults with Substantial Comorbidities (ALL-D 9 of 10).

[dd] The prognostic significance of MRD positivity may be regimen-, ALL subtype-, and/or ALL risk-dependent. MRD timepoints and levels prompting allogeneic HCT should be guided by the specific treatment protocol being used. In general, MRD positivity at the end of induction predicts high relapse rates and should prompt evaluation for allogeneic HCT. Therapy aimed at eliminating MRD prior to allogeneic HCT is preferred when possible (See Discussion).

[gg] See Supportive Care: Toxicity Management (ALL-C 2 of 4).

[hh] Although long-term remission after blinatumomab treatment is possible, allogeneic HCT should be considered as consolidative therapy.

[kk] Consider retesting for MRD at first available opportunity.

[ll] Blinatumomab can be considered for consolidation in patients induced with inotuzumab ozogamicin + mini-hyperCVD, or in patients for whom multiagent chemotherapy is contraindicated.

Surveillance

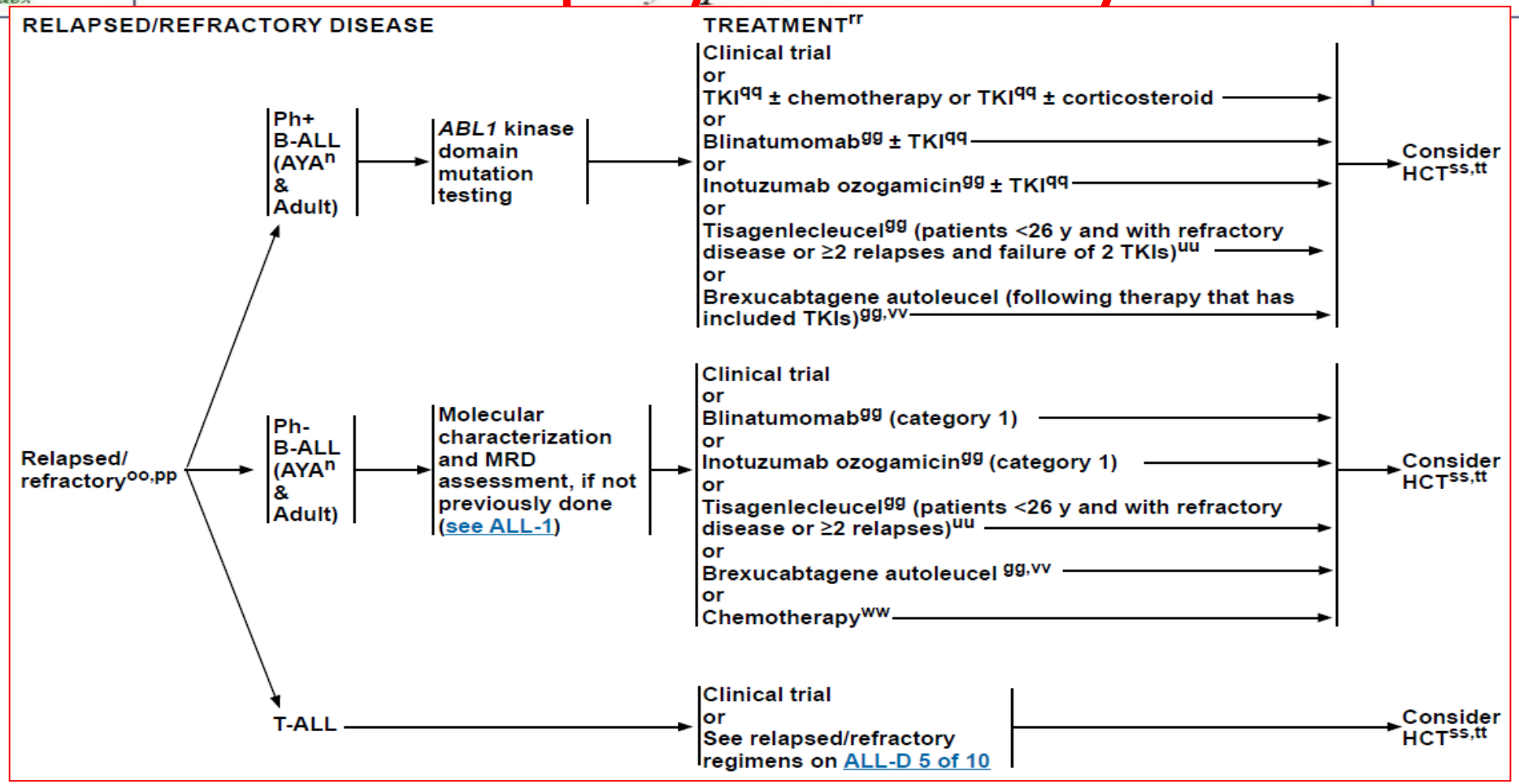
Year 1 (every 1–2 months):
- Physical exam, CBC with differential every month
- Liver function tests (LFTs) every 2 months until normal
- ~~Bone marrow aspirate, cerebrospinal fluid (CSF), and echocardiogram as indicated~~
  - ~~If bone marrow aspirate is done: Comprehensive cytogenetics, FISH, flow cytometry, and consideration of molecular tests~~

Year 2:
- Physical exam including testicular exam, CBC with differential every 3 months

Year 3+:
- Physical exam including testicular exam, CBC with differential every 6 months or as indicated

Other General Measures
- Bone marrow aspirate can be considered as clinically indicated at a frequency of up to 3 to 6 months for at least 5 years[nn]
  - If bone marrow aspirate is done: Flow cytometry with additional studies that may include comprehensive cytogenetics, FISH, molecular testing, and MRD assessment [See Minimal/Measurable Residual Disease Assessment (ALL-F)]
- Periodic *BCR-ABL1* transcript-specific quantification (Ph+ ALL)

Relapse/Refractory



[n] The ALL Panel considers AYA to be within the age range of 15–39 years. However, this age range is not a firm reference point because some of the recommended regimens have not been comprehensively tested across all ages.
[gg] See Supportive Care: Toxicity Management (ALL-C 2 of 4).
[oo] Isolated extramedullary relapse (both CNS and testicular) requires systemic therapy to prevent relapse in marrow.
[pp] See NCCN Guidelines for Palliative Care.
[qq] See Treatment Options Based on *BCR-ABL1* Mutation Profile (ALL-D 3 of 10).
[rr] See Principles of Systemic Therapy (ALL-D 3 of 10, ALL-D 4 of 10, and ALL-D 5 of 10).
[ss] If second remission is achieved prior to transplant and patient has not had a prior HCT, consolidative HCT is recommended.
[tt] For patients with relapsed disease after allogeneic HCT, a second allogeneic HCT and/or donor lymphocyte infusion (DLI) can be considered.
[uu] The role of allogeneic HCT following tisagenlecleucel is unclear. Persistence of tisagenlecleucel in peripheral blood and persistent B-cell aplasia has been associated with durable clinical responses without subsequent HCT. In the global registration trial, relapse-free survival was 59% at 12 months, with only 9% of patients proceeding to HCT.
[vv] See NCCN Guidelines for Management of Immunotherapy-Related Toxicities.
[ww] For patients in late relapse (>3 years from initial diagnosis), consider treatment with the same induction regimen (See ALL-D 2 of 10).

Supportive care

Best supportive care

- Infection control (See NCCN Guidelines for Prevention and Treatment of Cancer-Related Infections)
  - Prophylactic anti-infectives
    - Antibacterial prophylaxis: consider fluoroquinolones
    - Antiviral prophylaxis: HSV prophylaxis; VZV prophylaxis for at least 1 year after HSCT in transplant patients; and HBV prophylaxis for at least 6–12 months after HCT depending on HBV serology.
    - Cytomegalovirus (CMV) reactivation management: Consider CMV monitoring and pre-emptive therapy for all patients; for patients undergoing allogeneic HCT, CMV monitoring and pre-emptive therapy are strongly recommended until at least 6 months after transplantation.
    - Antifungal prophylaxis: Consider prophylaxis for all patients treated with chemotherapy; for patients undergoing allogeneic HSCT, antifungal prophylaxis is strongly recommended until at least day 75 after transplantation.
    - Pneumocystis pneumonia (PCP) prophylaxis[1]
  - Heightened awareness for risk of sepsis/death due to steroid therapy and neutropenia
  - Febrile neutropenia management
    - Fever is defined as a single temperature ≥38.3 °C (101°F) or ≥38.0 °C (100.4°F) over a 1-hour period
    - IV antibiotics/inpatient admission
- Acute TLS (See Tumor Lysis Syndrome in the NCCN Guidelines for Non-Hodgkin's Lymphomas)
- Pegaspargase Toxicity Management — see ALL-B 3 of 4 and ALL-B 4 of 4
- Methotrexate and Glucarpidase
  - Consider use of glucarpidase if significant renal dysfunction and methotrexate levels are >10 microM beyond 42–48 h. Leucovorin remains a component in the treatment of methotrexate toxicity and should be continued for at least 2 days following glucarpidase administration. However, be aware that leucovorin is a substrate for glucarpidase, and therefore should not be administered within two hours prior to or following glucarpidase.

Supportive care

Toxicity Management for Inotuzumab, Blinatumomab, Tisagenlecleucel, and Brexucabtagene Autoleucel

Inotuzumab Ozogamicin:

- Cytoreduction should be considered for those with WBC greater than 10,000 cells per microliter. On clinical trial, hydroxyurea or a combination of steroids and vincristine was used.
- Myelosuppression is common, and prophylactic antimicrobial strategies in accordance with institutional practice should be used.
- Liver enzymes, and particularly bilirubin, should be closely monitored, as sinusoidal obstruction syndrome (SOS) (or VOD) may occur, particularly among patients at higher risk (including those who are status-post allogeneic hematopoietic cell transplantation (HCT), those whose treatment extends beyond two cycles, and/or those who previously received or will receive double alkylator conditioning prior to allogeneic HCT. For those patients receiving inotuzumab as a bridge to allogeneic transplant, double alkylator conditioning is strongly discouraged. Ursodiol may be considered for VOD prophylaxis.

Blinatumomab:

- Cytoreduction should be considered for those with WBC greater than 15,000 cells per microliter, as high tumor burden may increase the risks of toxicity. On clinical trial, steroids were most commonly used.
- Patients should be monitored for cytokine release syndrome (CRS), a systemic inflammatory condition characterized by fever or hypothermia, that may progress to hypotension, hypoxia, and/or end organ damage. Infusion should be held with consideration for steroids and/or vasopressors for those with severe symptoms in accordance with manufacturer guidelines and prescriber information. Consider tocilizumab for patients with severe CRS.
- Because concurrent severe infection may mimic CRS, an evaluation for underlying infection and consideration of empiric antimicrobial therapy in accordance with institutional practice should be performed.
- Patients should be monitored for neurologic toxicity, which may include confusion, word-finding difficulty, somnolence, ataxia, tremor, seizure, or syncope. Infusion should be held with consideration of steroids for those with severe symptoms in accordance with manufacturer guidelines and prescribing information, and re-started (once symptoms have sufficiently improved) with dosing adjustments as per manufacturer guidelines and prescribing information.

Tisagenlecleucel/Brexucabtagene Autoleucel:

- Severe CRS and/or neurologic toxicity may accompany therapy, and should be managed in accordance with the manufacturer Risk Evaluation and Mitigation Strategies (REMS) program, to include tocilizumab (preferred for CRS) and steroids (preferred for tocilizumab-refractory CRS and/or neurologic toxicity).
- Prophylaxis with anti-seizure medication may be considered during the first month after chimeric antigen receptor [CAR] T-cell infusion.
- Severe neutropenia, T-cell depletion, and B-cell aplasia can occur, for which growth factor, prophylactic antimicrobial therapy, and intravenous (IV) immunoglobulin administration should be considered, in accordance with institutional practice.
- See NCCN Guidelines for Management of Immunotherapy-Related Toxicities.

CNS disease management

- Given the risks of neurotoxicity associated with central nervous system (CNS)-directed therapy, baseline and post-treatment comprehensive neuropsychological testing may be useful.
- The aim of CNS prophylaxis and/or treatment is to clear leukemic cells within sites that cannot be readily accessed by systemic chemotherapy due to the blood-brain barrier, with the overall goal of preventing CNS disease or relapse.
- Factors associated with increased risks for CNS leukemia in adults include mature B-cell immunophenotype, T-cell immunophenotype, high presenting WBC counts, and elevated serum LDH levels.[1,2]
- CNS involvement should be evaluated (by LP) at the appropriate timing:
  - Timing of LP should be consistent with the chosen treatment regimen.
  - Pediatric-inspired regimens typically include LP at the time of diagnostic workup.
  - The panel recommends that LP, if performed, be done concomitantly with initial IT therapy.
- Classification of CNS status:
  - CNS-1: No lymphoblasts in CSF regardless of WBC count.
  - CNS-2: WBC <5/mcL in CSF with presence of lymphoblasts.
  - CNS-3: WBC ≥5/mcL in CSF with presence of lymphoblasts.
  - If the patient has leukemic cells in the peripheral blood and the LP is traumatic and WBC ≥5/mcL in CSF with blasts, then compare the CSF WBC/RBC ratio to the blood WBC/RBC ratio. If the CSF ratio is at least two-fold greater than the blood ratio, then the classification is CNS-3; if not, then it is CNS-2.
- All patients with ALL should receive CNS prophylaxis. Although the presence of CNS involvement at the time of diagnosis is uncommon (about 3%–7%), a substantial proportion of patients (>50%) will eventually develop CNS leukemia in the absence of CNS-directed therapy.
- CNS-directed therapy may include cranial irradiation, IT chemotherapy (eg, methotrexate, cytarabine, corticosteroids), and/or systemic chemotherapy (eg, methotrexate, cytarabine, mercaptopurine, pegaspargase).
- CNS leukemia (CNS-3 and/or cranial nerve involvement) at diagnosis typically warrants treatment with cranial irradiation of 18 Gy. The recommended dose of radiation, where given, is highly dependent on the intensity of systemic chemotherapy; thus, it is critical to adhere to a given treatment protocol in its entirety. The entire brain and posterior half of the globe should be included. The inferior border should be below C2.
- Note that areas of the brain targeted by the radiation field in the management of ALL are different from areas targeted for brain metastases of solid tumors.
- With the incorporation of adequate systemic chemotherapy (eg, high-dose methotrexate, cytarabine) and IT chemotherapy regimens (eg, methotrexate alone or with cytarabine and a corticosteroid, which constitutes the triple IT regimen), it may be possible to avoid the use of upfront cranial irradiation except in cases of overt CNS leukemia at diagnosis, and to reserve the use of irradiation for relapsed/refractory therapy settings.
- Adequate systemic therapy should be given in the management of isolated CNS relapse.
- Patients with clinical evidence of testicular disease at diagnosis that is not fully resolved by the end of the induction therapy should be considered for radiation to the testes in the scrotal sac, which is typically done concurrently with the first cycle of maintenance chemotherapy. Testicular total dose should be 24 Gy.

Systemic chemotherapy options for Ph+ ALL

AYA Patients[g]:

Other Recommended Regimens
• EsPhALL regimen: TKI[h] + backbone of the Berlin-Frankfurt-Münster regimen (cyclophosphamide, vincristine, daunorubicin, dexamethasone, cytarabine, methotrexate, pegaspargase, and prednisone)[1-3]
• TKI[h] + hyper-CVAD (hyperfractionated cyclophosphamide, vincristine, doxorubicin, and dexamethasone), alternating with high-dose methotrexate, and cytarabine[4-8]
• TKI[h] + multiagent chemotherapy[9-13]
• TKI[h,15] + corticosteroid[i]
• TKI[h,j,14,15]
• TKI[h] + vincristine + dexamethasone[16]
• CALGB 10701 regimen: TKI[h] + multiagent chemotherapy (dexamethasone, vincristine, daunorubicin, methotrexate, etoposide, and cytarabine)[17]
• Blinatumomab ± TKI[h,k,18] (See ALL-3)

Adult Patients (<65 y and without substantial comorbidities):

Other Recommended Regimens
• TKI[h] + hyper-CVAD (hyperfractionated cyclophosphamide, vincristine, doxorubicin, and dexamethasone), alternating with high-dose methotrexate, and cytarabine[4-8]
• TKI[h] + multiagent chemotherapy[9-13]
• TKI[h,14,19] + corticosteroid[i]
• TKI[h,j,14,15,19]
• TKI[h] + vincristine + dexamethasone[16,20]
• CALGB 10701 regimen: TKI[h] + multiagent chemotherapy (dexamethasone, vincristine, daunorubicin, methotrexate, etoposide, and cytarabine)[17]
• Blinatumomab ± TKI[h,k,18,21] (See ALL-3)

For treatment of adult patients ≥65 years with ALL or adult patients with substantial comorbidities, see ALL-D 9 of 10.

Maintenance Regimens:

- **Add TKI[h] to maintenance regimen; optimal duration is unknown.**
- **Monthly vincristine/prednisone pulses (for 2–3 years). May include weekly methotrexate + daily 6-mercaptopurine (6-MP) as tolerated.[l,m]**

[a] For infection risk, monitoring, and prophylaxis recommendations for immune targeted therapies, see INF-A in the NCCN Guidelines for Prevention and Treatment of Cancer-Related Infections.
[b] All regimens include CNS prophylaxis with systemic therapy (eg, methotrexate, cytarabine) and/or IT therapy (eg, IT methotrexate, IT cytarabine; triple IT therapy with methotrexate, cytarabine, corticosteroid).
[c] There are data to support the benefit of rituximab in addition to chemotherapy for CD20-positive patients (especially in patients aged <60 years). However, there are no data to support giving rituximab concurrently with blinatumomab.
[d] An FDA-approved biosimilar is an appropriate substitute for rituximab.
[e] The specific drugs listed are primarily used in induction. For post-induction components, see listed references.
[f] For patients who develop hypersensitivity to E. coli-derived asparaginase, ERW or ERW-rywn can be substituted as a component of the multi-agent chemotherapeutic regimen to complete the full treatment course.
[g] The ALL Panel considers AYA to be within the age range of 15–39 years. However, this age range is not a firm reference point because some of the recommended regimens have not been comprehensively tested across all ages.
[h] TKI options include (in alphabetical order): bosutinib, dasatinib, imatinib, nilotinib, or ponatinib. Not all TKIs have been directly studied within the context of each specific regimen and the panel notes that there are limited data for bosutinib in Ph+ ALL. Use of a specific TKI should account for anticipated/prior TKI intolerance and disease-related features. For contraindicated mutations, see ALL-D 3 of 10.
[i] TKI + corticosteroid as induction should be followed by TKI + multiagent chemotherapy consolidation.
[j] TKI monotherapy is seldom effective as induction, however it may be considered as consolidation/maintenance in those unfit for additional therapies.
[k] For consolidation in MRD negative patients who are not candidates for multi-agent chemotherapy, and for consolidation in persistent/rising MRD.
[l] For patients receiving 6-MP, consider testing for *TPMT* gene polymorphisms, particularly in patients who develop severe neutropenia after starting 6-MP. Testing for both TPMT and NUDT15 variant status should be considered, especially for patients of East Asian origin. Relling MV, Schwab M, Whirl-Carrillo M, et al. Clinical pharmacogenetics implementation consortium guideline for thiopurine dosing based on TPMT and NUDT15 genotypes: 2018 update. Clin Pharmacol Ther 2019;105:1095-1105.
[m] Dose modifications for antimetabolites in maintenance should be consistent with the chosen treatment regimen. It may be necessary to reduce dose/eliminate antimetabolite in the setting of myelosuppression and/or hepatotoxicity.

Systemic chemotherapy options for Ph- ALL

AYA Patients[g]:

Preferred Regimens

- CALGB 10403 regimen: daunorubicin, vincristine, prednisone, and pegaspargase.[22,n,o]
- COG AALL0232 regimen: daunorubicin, vincristine, prednisone, and pegaspargase[n] (patients aged ≤21 years).[23,o]
- COG AALL0434 regimen with nelarabine (for T-ALL): daunorubicin, vincristine, prednisone, pegaspargase[n]; and nelarabine.[24,o]
- DFCI ALL regimen based on DFCI Protocol 00-01: doxorubicin, vincristine, prednisone, high-dose methotrexate, and pegaspargase.[25,n,o]

Other Recommended Regimens

- GRAALL-2005 regimen: daunorubicin, vincristine, prednisone, pegaspargase,[n] and cyclophosphamide (patients aged <60 years), with rituximab for CD20-positive disease.[26,o]
- PETHEMA ALL-96 regimen: daunorubicin, vincristine, prednisone, pegaspargase,[n] and cyclophosphamide (patients aged <30 years).[27,o]
- Hyper-CVAD: hyperfractionated cyclophosphamide, vincristine, doxorubicin, and dexamethasone, alternating with high-dose methotrexate and cytarabine; with rituximab for CD20-positive disease.[28]
- USC/MSKCC ALL regimen based on CCG-1882 regimen: daunorubicin, vincristine, prednisone, and methotrexate with augmented pegaspargase[n](patients aged 18–60 years).[29,30,o]
- Linker 4-drug regimen: daunorubicin, vincristine, pegaspargase,[n] and prednisone; with rituximab for CD20-positive disease.[31]
- Blinatumomab[p]

Adult Patients (<65 years and without substantial comorbidities):

Other Recommended Regimens

- CALGB 8811 Larson regimen: daunorubicin, vincristine, prednisone, pegaspargase,[n] and cyclophosphamide; for patients aged ≥60 years, reduced doses for cyclophosphamide, daunorubicin, and prednisone.[32,33]
- GRAALL-2005 regimen: daunorubicin, vincristine, prednisone, pegaspargase,[n] and cyclophosphamide (patients aged <60 years) with rituximab for CD20-positive disease.[26]
- Hyper-CVAD: hyperfractionated cyclophosphamide, vincristine, doxorubicin, and dexamethasone, alternating with high-dose methotrexate and cytarabine; with rituximab for CD20-positive disease.[28,34]
- USC/MSKCC ALL regimen based on CCG-1882 regimen: daunorubicin, vincristine, prednisone, and methotrexate with augmented pegaspargase[n] (patients aged <60 years).[29,30,o]
- Linker 4-drug regimen: daunorubicin, vincristine, prednisone, and pegaspargase[n]; with rituximab for CD20-positive disease (patients aged <60 years).[35]
- MRC UKALLXII/ECOG2993 regimen: daunorubicin, vincristine, prednisone, and pegaspargase[n] (induction phase I); and cyclophosphamide, cytarabine, and 6-MP[l,m] (induction phase II).[36]
- Blinatumomab[p]

For treatment of adult patients ≥65 years with ALL or adult patients with substantial comorbidities, see ALL 9 of 10.

Maintenance Regimen:

- Weekly methotrexate + daily 6-MP[l,m] + monthly vincristine/prednisone pulses (duration based on regimen)
- Blinatumomab alternating with POMP[l,m,q]

[a] For infection risk, monitoring, and prophylaxis recommendations for immune targeted therapies, see INF-A in the NCCN Guidelines for Prevention and Treatment of Cancer-Related Infections.
[b] All regimens include CNS prophylaxis with systemic therapy (eg, methotrexate, cytarabine) and/or IT therapy (eg, IT methotrexate, IT cytarabine; triple IT therapy with methotrexate, cytarabine, corticosteroid).
[c] There are data to support the benefit of rituximab in addition to chemotherapy for CD20-positive patients (especially in patients aged <60 years). However, there are no data to support giving rituximab concurrently with blinatumomab.
[d] An FDA-approved biosimilar is an appropriate substitute for rituximab.
[e] The specific drugs listed are primarily used in induction. For post-induction components, see listed references.
[f] For patients who develop hypersensitivity to E. coli-derived asparaginase, ERW or ERW-rywn can be substituted as a component of the multi-agent chemotherapeutic regimen to complete the full treatment course.
[g] The ALL Panel considers AYA to be within the age range of 15–39 years. However, this age range is not a firm reference point because some of the recommended regimens have not been comprehensively tested across all ages.
[l] For patients receiving 6-MP, consider testing for *TPMT* gene polymorphisms, particularly in patients who develop severe neutropenia after starting 6-MP. Testing for both TPMT and NUDT15 variant status should be considered, especially for patients of East Asian origin. Relling MV, Schwab M, Whirl-Carrillo M, et al. Clinical pharmacogenetics implementation consortium guideline for thiopurine dosing based on TPMT and NUDT15 genotypes: 2018 update. Clin Pharmacol Ther 2019;105:1095-1105.
[m] Dose modifications for antimetabolites in maintenance should be consistent with the chosen treatment regimen. It may be necessary to reduce dose/eliminate antimetabolite in the setting of myelosuppression and/or hepatotoxicity.
[n] Pegaspargase may be substituted with calaspargase pegol-mknl, an asparagine-specific enzyme, in patients ≤21 years for more sustained asparaginase activity. Silverman LB, et al. Blood 2016;128:175; Angiolillo AL, et al. J Clin Oncol 2014;32:3874-3882.
[o] Pediatric-inspired regimen.
[p] Blinatumomab can be considered for consolidation in MRD negative/unavailable if induced with inotuzumab ozogamicin + mini-hyperCVD, or in patients for whom multi-agent chemotherapy is contraindicated, and for consolidation in persistent/rising MRD.
[q] For maintenance in patients induced with inotuzumab ozogamicin + mini-hyperCVD.

Salvage chemotherapy for Ph+ ALL

PRINCIPLES OF SYSTEMIC THERAPY[a]
REGIMENS FOR RELAPSED OR REFRACTORY Ph-POSITIVE B-ALL[b,r]

Other Recommended Regimens

- TKI (dasatinib,[37,38] imatinib,[39] ponatinib,[40] nilotinib,[41] or bosutinib[42])
  - The TKIs noted above may also be used in combination with any of the induction regimens noted on ALL-D 1 of 10 that were not previously given.
- Blinatumomab ± TKI[43,44,t]
- Inotuzumab ozogamicin ± TKI[45,46,t]
- Tisagenlecleucel (patients aged <26 years and with refractory disease or ≥2 relapses and failure of 2 TKIs)[47,t,u]
- Brexucabtagene autoleucel (following therapy that has included TKIs)[48,t,u]
- The regimens listed on ALL-D 4 of 10 for Ph-negative B-ALL may be considered for Ph-positive B-ALL refractory to TKIs.

TREATMENT OPTIONS BASED ON *BCR-ABL1* MUTATION PROFILE

Therapy	Contraindicated Mutations[v]
Bosutinib	*T315I, V299L, G250E*, or *F317L*[w]
Dasatinib	*T315I/A, F317L/V/I/C*, or *V299L*
Nilotinib	*T315I, Y253H, E255K/V, or F359V/C/I* or *G250E*
Ponatinib[x]	None[s]

Regimens for Relapsed/Refractory Ph-Negative B-ALL

[a] For infection risk, monitoring, and prophylaxis recommendations for immune targeted therapies, see INF-A in the NCCN Guidelines for Prevention and Treatment of Cancer-Related Infections.

[b] All regimens include CNS prophylaxis with systemic therapy (eg, methotrexate, cytarabine) and/or IT therapy (eg, IT methotrexate, IT cytarabine; triple IT therapy with methotrexate, cytarabine, corticosteroid).

[r] The safety of relapsed/refractory regimens in adults 65 years and over or adults with substantial comorbidities has not been established. Please see ALL-D 9 of 10 for additional information.

[s] Ponatinib has activity against *T315I* mutations and is effective in treating patients with resistant or progressive disease on multiple TKIs. However, it is associated with a high frequency of serious vascular events (eg, strokes, heart attacks, tissue ischemia). The FDA indications are for the treatment of adult patients with *T315I*-positive, Philadelphia chromosome-positive acute lymphoblastic leukemia (Ph+ ALL) and for the treatment of adult patients with Ph+ ALL for whom no other TKI therapy is indicated. For details, see https://www.accessdata.fda.gov/drugsatfda_docs/label/2022/203469s035lbl.pdf.

[t] See Supportive Care: Toxicity Management (ALL-C 2 of 4).

[u] See NCCN Guidelines for Management of Immunotherapy-Related Toxicities.

[v] Mutations contraindicated for imatinib are too numerous to include. There are compound mutations that can cause resistance to ponatinib, but those are uncommon following treatment with bosutinib, dasatinib, or nilotinib.

[w] Nilotinib may be preferred over bosutinib in patients with *F317L* mutation.

[x] Ponatinib is a treatment option for patients with a *T315I* mutation and/or for patients for whom no other TKI is indicated.

References

Salvage chemotherapy for Ph- ALL

PRINCIPLES OF SYSTEMIC THERAPY[a]
REGIMENS FOR RELAPSED OR REFRACTORY Ph-NEGATIVE B-ALL[b,y]

Preferred Regimens
• Blinatumomab (for B-ALL only) (category 1)[44,s] • Inotuzumab ozogamicin (for B-ALL only) (category 1)[45,s] • Tisagenlecleucel (for B-ALL only) (patients aged <26 years and with refractory disease or ≥2 relapses)[47,s,u] • Brexucabtagene autoleucel (for B-ALL only)[48,s,u]
Other Recommended Regimens[r]
• Inotuzumab ozogamicin[s] + mini-hyperCVD ± blinatumomab[s] (for B-ALL only) (cyclophosphamide, dexamethasone, vincristine, methotrexate, cytarabine)[49,50] • Augmented hyper-CVAD: hyperfractionated cyclophosphamide, intensified vincristine, doxorubicin, intensified dexamethasone, and pegaspargase; alternating with high-dose methotrexate and cytarabine[51] • Vincristine sulfate liposome injection (VSLI)[52,53] • Clofarabine alone[54-57] or in combination (eg, clofarabine, cyclophosphamide, etoposide[55,58,59]) • MOpAD regimen (for R/R Ph-negative ALL only): methotrexate, vincristine, pegaspargase, dexamethasone; with rituximab[d] for CD20-positive disease[60] • Fludarabine-based regimens ▸ FLAG-IDA: fludarabine, cytarabine, granulocyte colony-stimulating factor, ± idarubicin[61] ▸ FLAM: fludarabine, cytarabine, and mitoxantrone[62] • Cytarabine-containing regimens: eg, high-dose cytarabine, idarubicin, IT methotrexate[63] • Alkylator combination regimens: eg, etoposide, ifosfamide, mitoxantrone[64]

REGIMENS FOR RELAPSED OR REFRACTORY Ph-NEGATIVE T-ALL[b,r,y]

Preferred Regimens
• Nelarabine[65-68] ± etoposide and cyclophosphamide[69-71]
Other Recommended Regimens
• Bortezomib[72] + chemotherapy • Daratumumab (Category 2B)[73-77] • HiDAC: high-dose cytarabine[78,79] • Mitoxantrone, etoposide, and cytarabine[80] • Venetoclax + chemotherapy (eg, decitabine, hyper-CVAD, nelarabine, mini-hyper-CVD) (Category 2B)[81-84] • The regimens listed on ALL-D 4 of 10 for relapsed/refractory Ph-negative B-ALL may be appropriate/considered for R/R T-ALL.

[a] For infection risk, monitoring, and prophylaxis recommendations for immune targeted therapies, see INF-A in the NCCN Guidelines for Prevention and Treatment of Cancer-Related Infections.
[b] All regimens include CNS prophylaxis with systemic therapy (eg, methotrexate, cytarabine) and/or IT therapy (eg, IT methotrexate, IT cytarabine; triple IT therapy with methotrexate, cytarabine, corticosteroid).
[d] An FDA-approved biosimilar is an appropriate substitute for rituximab.
[r] The safety of relapsed/refractory regimens in adults 65 years and over or adults with substantial comorbidities has not been established. Please see ALL-D 9 of 10 for additional information.
[s] See Supportive Care: Toxicity Management (ALL-C 2 of 4).
[u] See NCCN Guidelines for Management of Immunotherapy-Related Toxicities.
[y] For patients in late relapse (>3 years from initial diagnosis), consider treatment with the same induction regimen (See ALL-D 2 of 10).

Taipei Veterans General Hospital Practice Guidelines Hematology

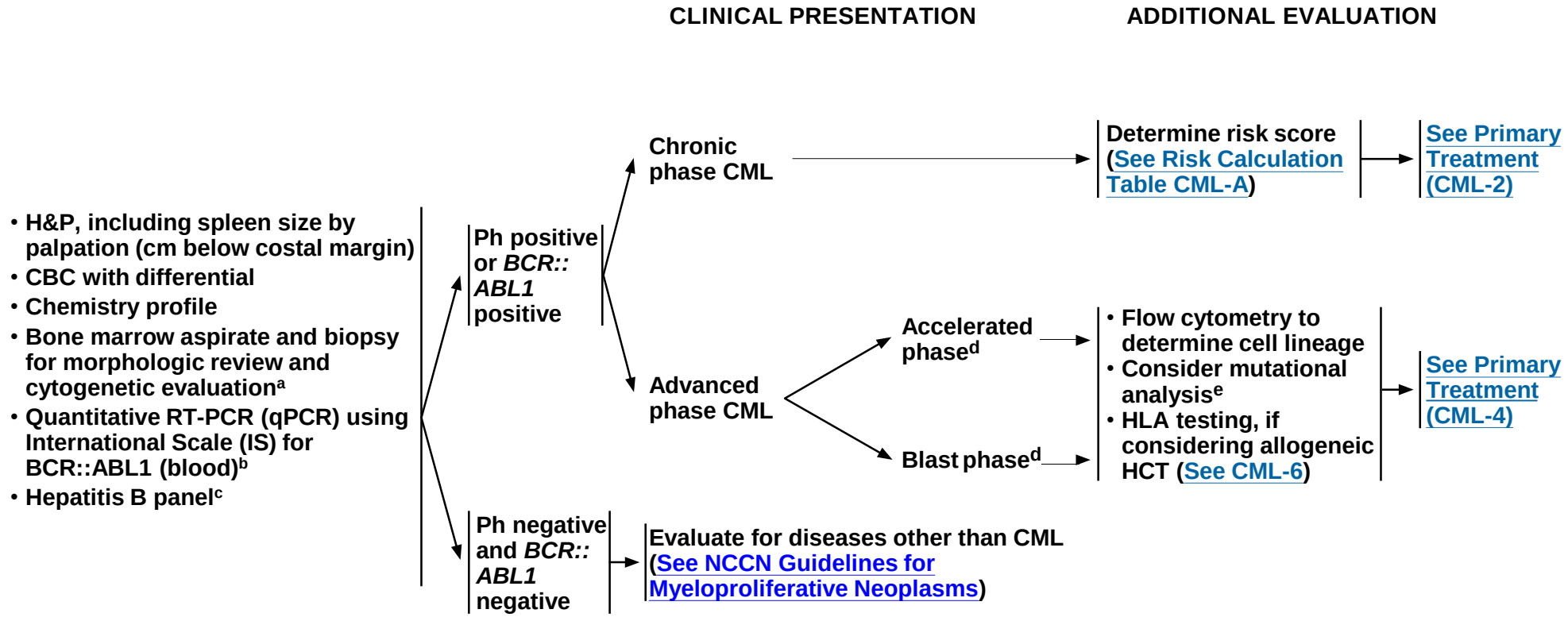
Chronic Myeloid Leukemia

Chronic myeloid leukemia

- WHO 5th edition
  - Classification of myeloid and histiocytic/dendritic neoplasms follows the Human Genome Organization Gene Nomenclature Committee
  - New designation of gene fusions using double colon marks (::)
    - bcr-abl1 => bcr::abl1
  - A single colon (:) => indicate a chromosome break
  - A double colon (::) to denote *break and reunion*

Leukemia volume 35, pages3040–3043 (2021)

Initial work-up for CML



a Bone marrow evaluation ~~is recommended~~ should be done for the initial workup, to provide morphologic review, and also to detect chromosomal abnormalities in addition to the Ph chromosome. Fluorescence in situ hybridization (FISH) can be used if cytogenetic evaluation is not possible.

b Consider qualitative RT-PCR for the detection of atypical BCR::ABL1 transcripts. See Discussion. Referral to centers with expertise in the management of rare hematologic malignancies is recommended.

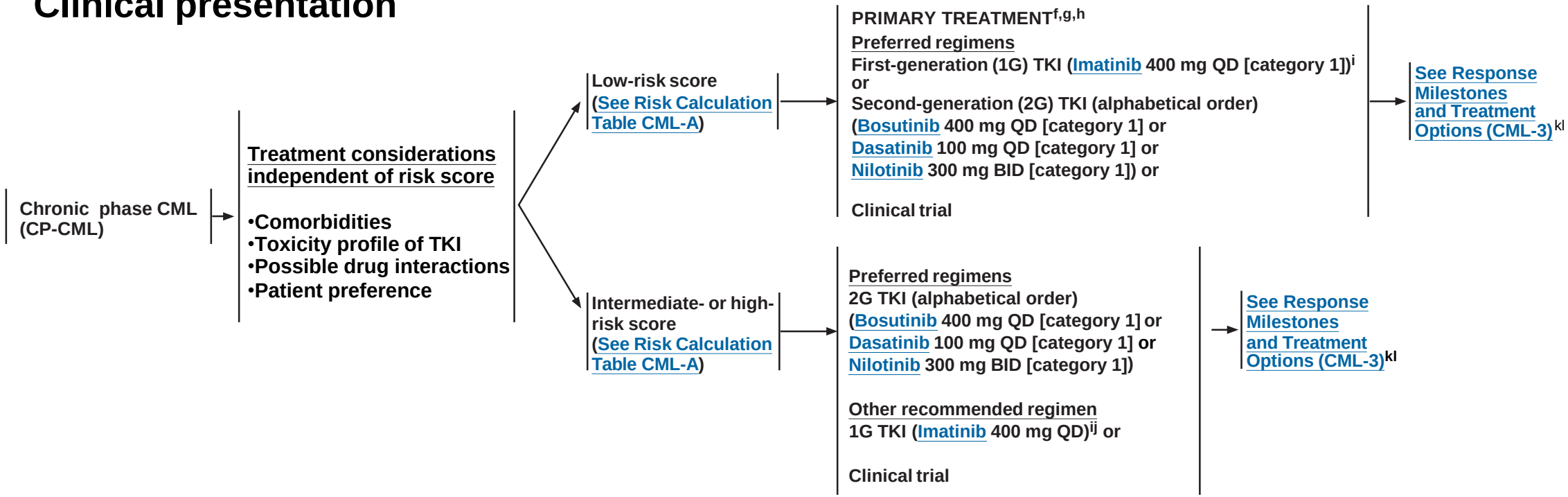
c Hepatitis B virus reactivation has been reported in patients receiving tyrosine kinase inhibitor (TKI) therapy. However, it is not always possible to reliably estimate the frequency or establish a relationship to drug exposure because these incidences are reported voluntarily from a population of uncertain size.

d See Definitions of Accelerated Phase and Blast Phase (CML-B).

e Consider myeloid mutation panel for patients with accelerated phase or blast phase. (NGS in detection of low-level mutations in 236 consecutive patients with CML and inadequate response to TKI therapy)

Chronic myeloid leukemia

Clinical presentation



[f] If treatment is needed during pregnancy, it is preferable to initiate treatment with interferons (interferon alfa-2a or peginterferon alfa-2a). Interferon alfa-2a/2b and peginterferon alfa-2b have been discontinued. Peginterferon alfa-2a may be substituted for other interferon preparations. TKI therapy, particularly during the first trimester, should be avoided. See Management of CML During Pregnancy (CML-C).

[g] Based on follow-up data from the BFORE, DASISION, and ENESTnd trials, 2G TKIs (bosutinib, dasatinib, or nilotinib) are preferred for patients with an intermediate- or high-risk score. 2G TKIs should also be considered for specific subgroups (based on the assessment of treatment goals and benefit/risks), for example, younger patients who are interested in ultimately discontinuing treatment and especially young patients assigned female at birth whose goal is to achieve a deep and rapid molecular response and eventual discontinuation of TKI therapy for family planning purposes.

[h] Limited available evidence from small cohort studies suggests that initiation of first-line TKIs (bosutinib, dasatinib, or nilotinib) at lower doses (to minimize treatment- related adverse events) and dose reduction (with close monitoring) in patients who achieve optimal responses are appropriate strategies to reduce the risk of long- term toxicities. However, the minimum effective dose or optimal de-escalation of TKI (bosutinib, dasatinib, or nilotinib) has not yet been established in prospective randomized clinical trials. See the Discussion section for *Dose Modifications of TKI Therapy* (MS-17).

[i] Innovator and generic drugs approved by the regulatory authorities based on pharmacokinetic equivalence can be used interchangeably. An FDA-approved generic version is an appropriate substitute for an innovator drug (imatinib). Generic versions of other TKIs are likely to be marketed in the near future.

[j] Imatinib may be preferred for older patients with comorbidities such as cardiovascular disease.

[k] See Criteria for Response and Relapse (CML-D).

[l] See Monitoring Response to TKI Therapy and Mutational Analysis (CML-E).

Chronic myeloid leukemia

EARLY TREATMENT RESPONSE MILESTONES[k,l]

BCR-ABL1 (IS)	3 months	6 months	12 months[l]
>10%[m]	YELLOW	RED	
>1%–10%	GREEN		YELLOW
>0.1%–1%	GREEN		LIGHT GREEN
≤0.1%	GREEN		

COLOR	CONCERN	CLINICAL CONSIDERATIONS	SECOND-LINE TREATMENT
RED	TKI-resistant disease	• Evaluate patient compliance and drug interactions • Consider BCR::ABL1 kinase domain mutational analysis	Switch to alternate TKI (CML-5) and evaluate for allogeneic HCT
YELLOW	Possible TKI resistance	• Evaluate patient compliance and drug interactions • Consider BCR::ABL1 kinase domain mutational analysis • Consider bone marrow cytogenetic analysis to assess for MCyR at 3 mo or CCyR at 12 mo	Switch to alternate TKI (CML-5) or Continue same TKI (other than imatinib) [p] and Consider evaluation for allogeneic HCT
Light green	TKI-sensitive disease	• If treatment goal is long-term survival: ~~>0.1%~~ <1% optimal • If treatment goal is treatment-free remission: ≤ 0.1% optimal	• If optimal: continue same TKI • If not optimal: shared decision-making with patient[q,r]
GREEN	TKI-sensitive disease	• Monitor response (CML-D) and side effects	Continue same TKI [s]

[k] See Criteria for Response and Relapse (CML-D).

[l] See Monitoring Response to TKI Therapy and Mutational Analysis (CML-E).

[m] *BCR::ABL1* ≤0.1% at 12 months is associated with a very low probability of subsequent loss of response and a high likelihood of achieving a subsequent deep molecular response (DMR MR4.0; ≤0.01% *BCR::ABL1* IS), which is a prerequisite for a trial of treatment-free remission (TFR).

[n] Patients with *BCR::ABL1* only slightly >10% at 3 months and/or with a steep decline from baseline may achieve <10% at 6 months and have generally favorable outcomes. Therefore, it is important to interpret the value at 3 months in this context before making drastic changes to the treatment strategy

[o] Consider myeloid mutation panel to identify *BCR::ABL1*–independent resistance mutations in patients with no BCR::ABL1 kinase domain mutations.

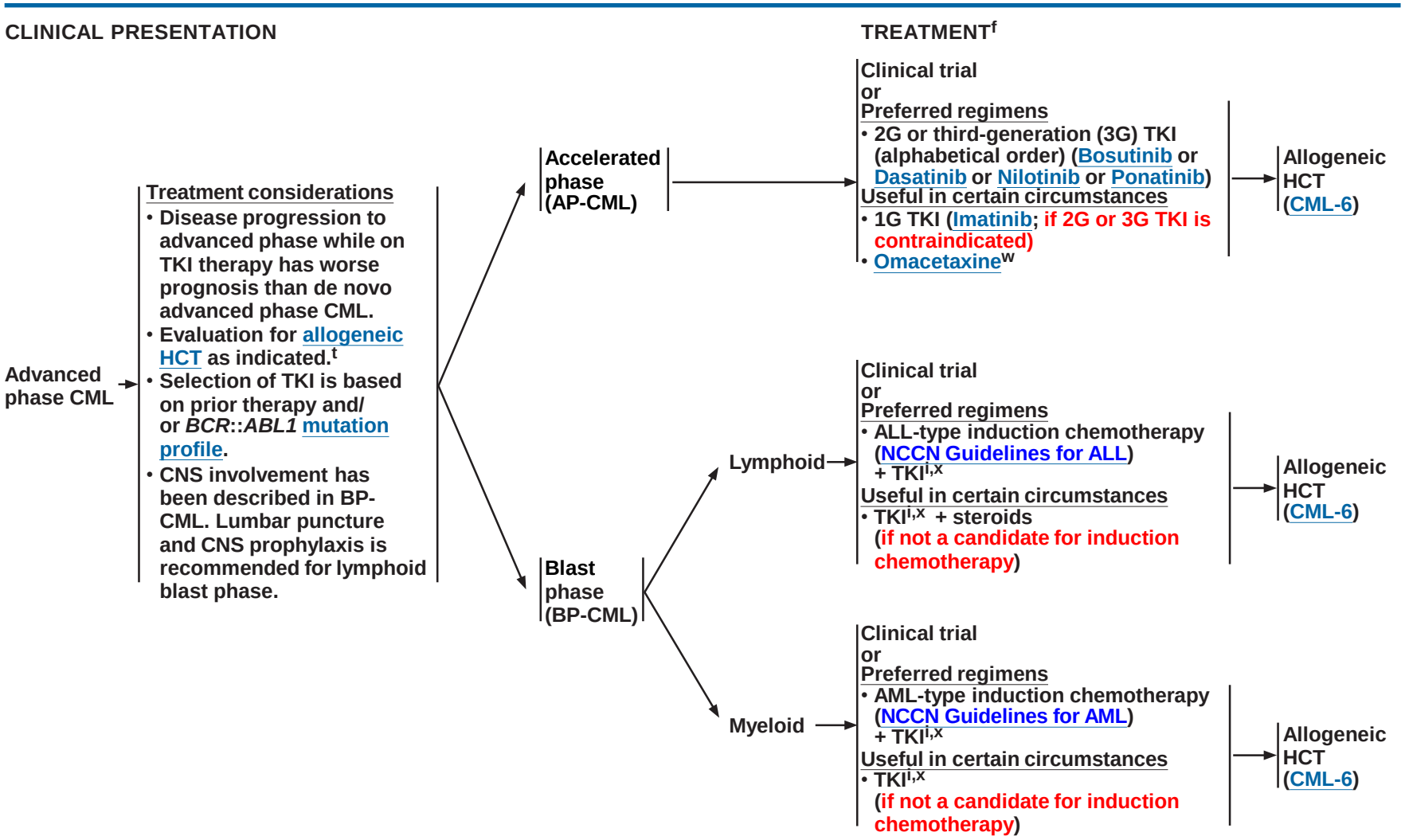
[p] Achievement of response milestones must be interpreted within the clinical context. Patients with more than 50% reduction compared to baseline or minimally above the 10% cutoff can continue the same dose of dasatinib, nilotinib, or bosutinib for another 3 months. Continuation of imatinib 400 mg is not recommended.

[q] Switching from imatinib to a 2G TKI improves response, but is associated with increased toxicity.

[r] Consider referral to a specialized CML center and/or enrollment in a clinical trial.

[s] Discontinuation of TKI with careful monitoring is feasible in selected patients. See Discontinuation of TKI Therapy (CML-F).

Chronic myeloid leukemia



TREATMENT RECOMMENDATIONS BASED ON *BCR*::*ABL1* MUTATION PROFILE

- **Patients with disease resistant to primary treatment with imatinib should be treated with bosutinib, dasatinib, or nilotinib in the second-line setting, taking into account BCR::ABL1 kinase domain mutation status.**
- **Patients with disease resistant to primary treatment with bosutinib, dasatinib, or nilotinib can be treated with an alternate TKI (other than imatinib) in the second-line setting, taking into account BCR::ABL1 kinase domain mutation status. The durability of these responses is frequently limited.**
- **The table below lists the BCR::ABL1 kinase domain mutations that should NOT be treated with asciminib, bosutinib, dasatinib, or nilotinib.**

THERAPY	CONTRAINDICATED MUTATIONS[z]
Asciminib[y]	A337T or P465S
Bosutinib	T315I, V299L, G250E, or F317L[aa]
Dasatinib	T315I/A, F317L/V/I/C, or V299L
Nilotinib	T315I, Y253H, E255K/V, or F359V/C/I
Ponatinib,[bb] Omacetaxine,[cc] allogeneic HCT (CML-6), or clinical trial	None

[y] Asciminib is a treatment option for CP-CML patients with the T315I mutation and/or CP-CML with resistance or intolerance to at least two prior TKIs.

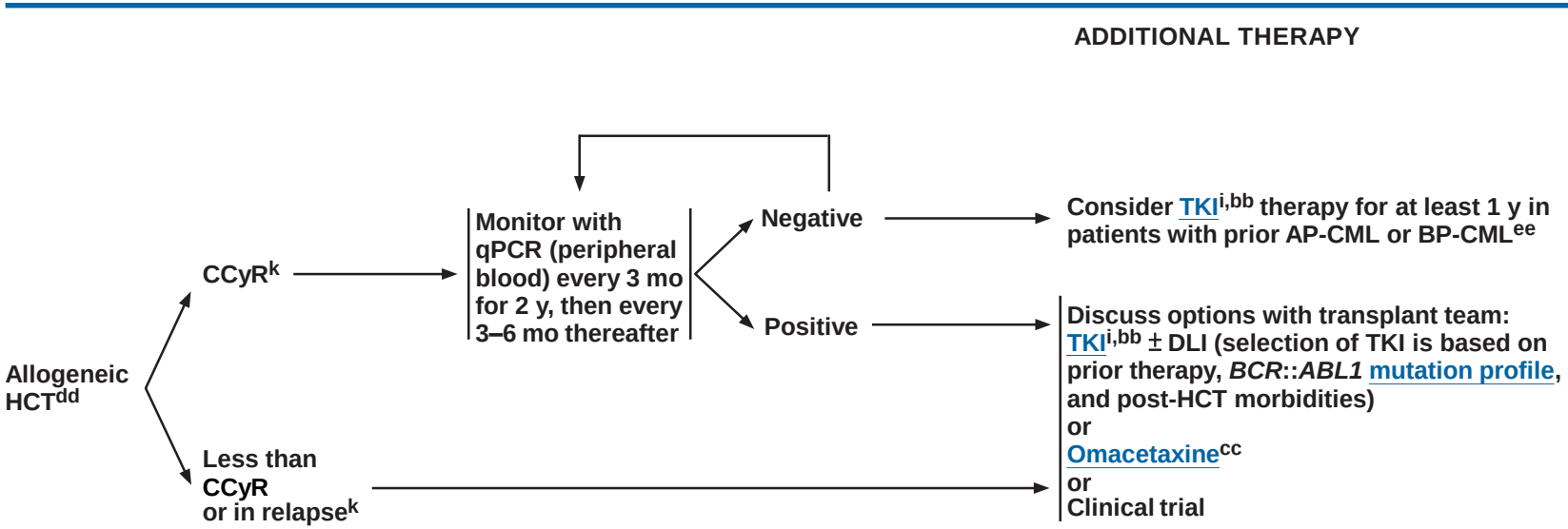
[z] Mutations contraindicated for imatinib are too numerous to include. BCR::ABL35$_{INS}$ has been reported in patients who do not respond to imatinib; however, there are not enough data to confirm that 2G TKIs could overcome this resistance (Berman E, et al. Leuk Res 2016;49:108-112). See Discussion.

[aa] Bosutinib has minimal activity against an F317L mutation. Nilotinib may be preferred over bosutinib in patients with an F317L mutation.

[bb] Ponatinib is the preferred treatment option for patients with a T315I mutation. It is also a treatment option for CP-CML with resistance or intolerance to at least two prior TKIs or for patients with AP-CML or BP-CML for whom no other TKI is indicated. There are compound mutations that can cause resistance to ponatinib, but those are uncommon following treatment with bosutinib, dasatinib, or nilotinib.

[cc] Omacetaxine is a treatment option for patients with chronic or accelerated phase CML that is resistant and/or intolerant to two or more TKIs.

Chronic myeloid leukemia



[i] Innovator and generic drugs approved by the regulatory authorities based on pharmacokinetic equivalence can be used interchangeably. An FDA-approved generic version is an appropriate substitute for an innovator drug (imatinib). Generic versions of other TKIs are likely to be marketed in the near future.

[k] See Criteria for Response and Relapse (CML-D).

[bb] Ponatinib is the preferred treatment option for patients with a T315I mutation. It is also a treatment option for CP-CML with resistance or intolerance to at least two prior TKIs or for patients with AP-CML or BP-CML for whom no other TKI is indicated. There are compound mutations that can cause resistance to ponatinib, but those are uncommon following treatment with bosutinib, dasatinib, or nilotinib.

[cc] Omacetaxine is a treatment option for patients with chronic or accelerated phase CML that is resistant and/or intolerant to two or more TKIs.

[dd] Indications for allogeneic HCT: advanced phase CML at presentation or disease progression to blast phase. Outcomes of allogeneic HCT are dependent on age, comorbidities, donor type, and transplant center.

[ee] Carpenter PA, et al. Blood 2007;109:2791-2793; Olavarria E, et al. Blood 2007;110:4614-4617; DeFilipp Z, et al. Clin Lymphoma Myeloma Leuk 2016;16:466-471.

RISK CALCULATION TABLE

Risk Score	Calculation	Risk Category	
Sokal score[1]	Exp 0.0116 x (age - 43.4) + 0.0345 x (spleen - 7.51) + 0.188 x [(platelet count ÷ 700)^2 - 0.563] + 0.0887 x (blasts - 2.10)	Low Intermediate High	<0.8 0.8 – 1.2 >1.2
Hasford (EURO) score[2]	(0.6666 x age [0 when age <50 years; 1, otherwise] + 0.042 x spleen size [cm below costal margin] + 0.0584 × percent blasts + 0.0413 × percent eosinophils + 0.2039 × basophils [0 when basophils <3%; 1, otherwise] + 1.0956 × platelet count [0 when platelets <1500 × 10^9/L; 1, otherwise]) × 1000	Low Intermediate High	≤780 >780 – ≤1480 >1480
EUTOS long-term survival (ELTS) score[3]	0.0025 × (age/10)^3 + 0.0615 × spleen size cm below costal margin + 0.1052 × blasts in peripheral blood + 0.4104 × (platelet count/1000)$^{-0.5}$	Low Intermediate High	≤1.5680 >1.5680 but ≤2.2185 >2.2185

Calculation of relative risk based on Sokal or Hasford (EURO) score can be found at: https://www.leukemia net.org/content/leukemias/cml/euro and_sokal_score/index_eng.html

Online calculator for the ELTS score can be found at: https://www.leukemia-net.org/content/leukemias/cml/elts_score/index_eng.html

1 Sokal J, Cox EB, Baccarani M, et al. Prognostic discrimination in "good-risk" chronic granulocytic leukemia. Blood 1984;63:789-799.
2 Hasford J, Pfirrmann M, Hehlmann R, et al. A new prognostic score for survival of patients with chronic myeloid leukemia treated with interferon alfa. Writing Committee for the Collaborative CML Prognostic Factors Project Group. J Natl Cancer Inst 1998;90:850-858.
3 Pfirrman M, Baccarani M, Saussele S, et al. Prognosis of long-term survival considering disease-specific death in patients with chronic myeloid leukemia. Leukemia 2016;30:48-56.

Chronic myeloid leukemia

DEFINITIONS OF ACCELERATED PHASE[1,2]

Modified MD Anderson Cancer Center (MDACC) Criteria[3,4] (most commonly used in clinical trials)
• Peripheral blood myeloblasts ≥15% and <30% • Peripheral blood myeloblasts and promyelocytes combined ≥30% • Peripheral blood basophils ≥20% • Platelet count ≤100 x 10^9/L unrelated to therapy • Additional clonal cytogenetic abnormalities in Ph+ cells[5]

DEFINITIONS OF BLAST PHASE[1]

International Bone Marrow Transplant Registry[6,7]
• ≥30% blasts in the blood, marrow, or both • Extramedullary infiltrates of leukemic cells

1 Any increase in lymphoblasts is concerning for (nascent) blast phase.

2 Sokal criteria (Sokal JE, Baccarani M, Russo D, Tura S. Staging and prognosis in chronic myelogenous leukemia. Semin Hematol 1988;25:49-61) and IBMTR criteria (Savage DG, Szydlo RM, Chase A, et al. Bone marrow transplantation for chronic myeloid leukemia: The effects of differing criteria for defining chronic phase on probabilities of survival and relapse. Br J Haematol 1997;99:30-35) are historically used when HCT is the recommended treatment option.

3 Kantarjian HM, Deisseroth A, Kurzrock R, et al. Chronic myelogenous leukemia: A concise update. Blood 1993;82:691-703.

4 Talpaz M, Silver RT, Druker BJ, et al. Imatinib induces durable hematologic and cytogenetic responses in patients with accelerated phase chronic myeloid leukemia: results of a phase 2 study. Blood 2002;99:1928-1937.

5 The prognostic significance of additional chromosomal abnormalities in Ph-positive cells (ACA/Ph+) is related to the specific chromosomal abnormality and often other features of accelerated phase. The presence of "major route" ACA/Ph+ (trisomy 8, isochromosome 17q, second Ph, and trisomy 19) at diagnosis may have a negative prognostic impact on survival.

6 Druker BJ. Chronic Myelogenous Leukemia In: DeVita VT, Lawrence TS, Rosenburg SA, eds. DeVita, Hellman, and Rosenberg's Cancer: Principles & Practice of Oncology. Vol. 2 (ed 8): Lippincott, Williams and Wilkins; 2007:2267-2304.

7 World Health Organization (WHO) criteria may be included in some reports (Swerdlow SH, Harris NL, Jaffe ES, et al. WHO Classification of Tumours of Haematopoietic and Lymphoid Tissues. Revised 4th ed. Lyon, France: IARC; 2017): blasts ≥20% of peripheral white blood cells or of nucleated bone marrow cells; extramedullary blast proliferation; and large foci or clusters of blasts in the bone marrow biopsy. However, it should be noted that modified MDACC criteria were used in most clinical trials leading to the approval of TKIs.

MANAGEMENT OF CML DURING PREGNANCY

TKI Therapy and Conception

- TKI therapy appears to affect some male hormones at least transiently, but does not appear to have a deleterious effect on male fertility; miscarriage or fetal abnormality rate is not elevated in female partners of male patients on TKI therapy.
- TKI therapy during pregnancy in patients assigned female at birth has been associated with both a higher rate of miscarriage and fetal abnormalities. A prolonged washout period prior to pregnancy, prompt consideration of holding TKI therapy (if pregnancy occurs while on TKI therapy), and close monitoring should be considered.
- Discontinuation of TKI therapy because of pregnancy in patients who were not in DMR (≥MR4.0; ≤0.01% BCR::ABL1 IS) has only been reported in a small series of patients. Conception while on active TKI therapy is strongly discouraged due to the risk of fetal abnormalities.
- Prior to attempting pregnancy, patients of childbearing age and their partners should be counseled about the potential risks and benefits of discontinuation of TKI therapy and possible resumption of TKI therapy should CML recur during pregnancy. Fertility preservation should be discussed with all patients of childbearing age prior to the initiation of TKI therapy. Referral to a CML specialty center and consultation with a high- risk obstetrician is recommended.

Chronic myeloid leukemia

MANAGEMENT OF CML DURING PREGNANCY

Treatment and Monitoring During Pregnancy

- In patients assigned male at birth, TKI therapy need not be discontinued if a pregnancy is planned. Sperm banking can also be performed prior to starting TKI therapy, although there are no data regarding the quality of sperm in patients with untreated CML.
- In patients assigned female at birth, TKI therapy should be stopped prior to natural conception, and patients should remain off therapy during pregnancy. Referral to an in vitro fertilization (IVF) center is recommended in coordination with the patient's obstetrician. TKI should be stopped prior to attempting a natural pregnancy or oocyte retrieval, but the optimal timing of discontinuation is unknown.
- The use of TKI therapy, particularly during the first trimester, should be avoided. If TKI therapy is considered during pregnancy, the potential risks and benefits must be carefully evaluated in terms of maternal health and fetal risk on an individual basis prior to initiation of TKI therapy during pregnancy.
- If treatment is needed, it is preferable to initiate treatment with interferons.
  Both interferon alfa-2a or peginterferon alfa-2a have been used during pregnancy. Most of the data using interferons during pregnancy have been reported in patients with essential thrombocythemia.
  If introduced earlier, the use of interferon alfa-2a or peginterferon alfa-2a can preserve molecular remission after discontinuation of TKI. Interferon alfa-2a/2b and peginterferon alfa-2b have been discontinued.
  Peginterferon alfa-2a may be substituted for other interferon preparations.
- The panel recommends against the use of hydroxyurea during pregnancy, especially in the first trimester, if possible.
- Leukapheresis can be used for a rising white blood cell (WBC) count, although there are no data that recommend at what level of WBC count leukapheresis should be initiated.
- Low-dose aspirin or low-molecular-weight heparin can be considered for patients with thrombocytosis.
- Monthly monitoring with qPCR and initiating treatment if the BCR::ABL1 IS increases to >1.0% is recommended.

Breastfeeding

- TKI therapy can be restarted after delivery. However, patients should be advised not to breastfeed while on TKI therapy, as TKIs pass into human breast milk.
- Breastfeeding without TKI therapy may be safe with molecular monitoring, but preferably in those patients with CML who have achieved durable DMR. It may be acceptable to avoid TKIs for the short period of the first 2–5 days after labor to give the child colostrum.
- Close molecular monitoring is recommended for patients who extend the treatment-free period for breastfeeding. If the loss of MMR after treatment cessation is confirmed, breastfeeding needs to be terminated and TKI therapy should be restarted.

Chronic myeloid leukemia

CRITERIA FOR RESPONSE AND RELAPSE

Response/Relapse	Definition
Complete hematologic response (CHR)[1]	• Complete normalization of peripheral blood counts with leukocyte count <10 x 10^9/L • Platelet count <450 x 10^9/L • No immature cells, such as myelocytes, promyelocytes, or blasts in peripheral blood • No signs and symptoms of disease with resolution of palpable splenomegaly
Cytogenetic response[2,3]	• **Complete cytogenetic response (CCyR):** No Ph-positive metaphases[4] • **Major cytogenetic response (MCyR):** 0%–35% Ph-positive metaphases • **Partial cytogenetic response (PCyR):** 1%–35% Ph-positive metaphases • **Minor cytogenetic response:** >35%–65% Ph-positive metaphases
Molecular response[5,6,7]	• **Early molecular response (EMR):** *BCR::ABL1* (IS) ≤10% at 3 and 6 months • **Major molecular response (MMR):** *BCR::ABL1* (IS) ≤0.1% or ≥3-log reduction in *BCR::ABL1* transcripts from the standardized baseline, if qPCR (IS) is not available • **Deep molecular response (DMR): MR4.0:** *BCR::ABL1* (IS) ≤0.01% or **MR4.5:** *BCR::ABL1* (IS) ≤0.0032%
Relapse	• Any sign of loss of hematologic response • Any sign of loss of CCyR or its molecular response correlate defined as an increase in *BCR::ABL1* transcript to >1%[4] • 1-log increase in *BCR::ABL1* transcript levels with loss of MMR[8]

1 Faderl S, Talpaz M, Estrov Z, Kantarjian HM. Chronic myelogenous leukemia: biology and therapy. Ann Intern Med 1999;131:207-219. The American College of Physicians-American Society of Internal Medicine is not responsible for the accuracy of the translation.
2 A minimum of 20 metaphases should be examined.
3 O'Brien SG, Guilhot F, Larson RA, et al. Imatinib compared with interferon and low-dose cytarabine for newly diagnosed chronic-phase chronic myeloid leukemia. N Engl J Med 2003;348:994-1004.
4 CCyR correlates with ***BCR::ABL1*** (IS) ≤1%.
5 Hughes TP, Kaeda J, Branford S, et al. Frequency of major molecular responses to imatinib or interferon alfa plus cytarabine in newly diagnosed chronic myeloid leukemia. N Engl J Med 2003;349:1423-1432.
6 Hughes T, Deininger M, Hochhaus A, et al. Monitoring CML patients responding to treatment with tyrosine kinase inhibitors: review and recommendations for harmonizing current methodology for detecting BCR-ABL transcripts and kinase domain mutations and for expressing results. Blood 2006;108:28-37.
7 Cross NC, White HE, Müller MC, Saglio G, Hochhaus A. Standardized definitions of molecular response in chronic myeloid leukemia. Leukemia 2012;26:2172-2175.
8 The loss of MMR in the presence of a CCyR does not necessarily constitute treatment failure.

Chronic myeloid leukemia

MONITORING RESPONSE TO TKI THERAPY AND MUTATIONAL ANALYSIS

Test	Recommendation
Bone marrow cytogenetics[1]	• At diagnosis • Failure to reach response milestones • Any sign of loss of hematologic response • Any sign of loss of CCyR or its molecular response correlate defined as an increase in *BCR::ABL1* transcript to >1%
qPCR using IS	• At diagnosis • Every 3 months after initiating treatment. After *BCR::ABL1* (IS) ≤1%[2] has been achieved, every 3 months for 2 years and every 3–6 months thereafter • If there is a 1-log increase in *BCR::ABL1* transcript levels with MMR, qPCR should be repeated in 1–3 months
BCR::ABL1 kinase domain mutation analysis	• Chronic phase[3] ▸ Failure to reach response milestones ▸ Any sign of loss of hematologic response ▸ Any sign of loss of CCyR or its molecular response correlate defined as an increase in *BCR::ABL1* transcript to >1% ▸ 1-log increase in *BCR::ABL1* transcript levels and loss of MMR • Disease progression to accelerated or blast phase[3]

1 FISH has been inadequately studied for monitoring response to treatment.
2 CCyR correlates with *BCR::ABL1* (IS) ≤1%.
3 Consider myeloid mutation panel to identify *BCR::ABL1* – independent resistance mutations in patients with no BCR::ABL1 kinase domain mutations.

DISCONTINUATION OF TKI THERAPY

General Considerations

- Discontinuation of TKI therapy appears to be safe in select patients with CML.
- Consult with a CML specialist to review the appropriateness for TKI discontinuation and potential risks and benefits of treatment discontinuation, including TKI withdrawal syndrome.
- Clinical studies that have evaluated the safety and efficacy of TKI discontinuation have employed strict eligibility criteria and have mandated more frequent molecular monitoring than typically recommended for patients on TKI therapy.
- Some patients have experienced significant adverse events that are believed to be due to TKI discontinuation.
- Discontinuation of TKI therapy should only be performed in consenting patients after a thorough discussion of the potential risks and benefits.
- Consultation with an center of expertise is recommended in the following circumstances:
  - Any significant adverse event is believed to be related to treatment discontinuation.
  - There is progression to AP-CML or BP-CML at any time.
  - There is failure to regain MMR after 3 months following treatment re-initiation.
- Outside of a clinical trial, discontinuation of TKI therapy should be considered only if ALL of the criteria included in the list below are met.

Criteria for TKI Discontinuation

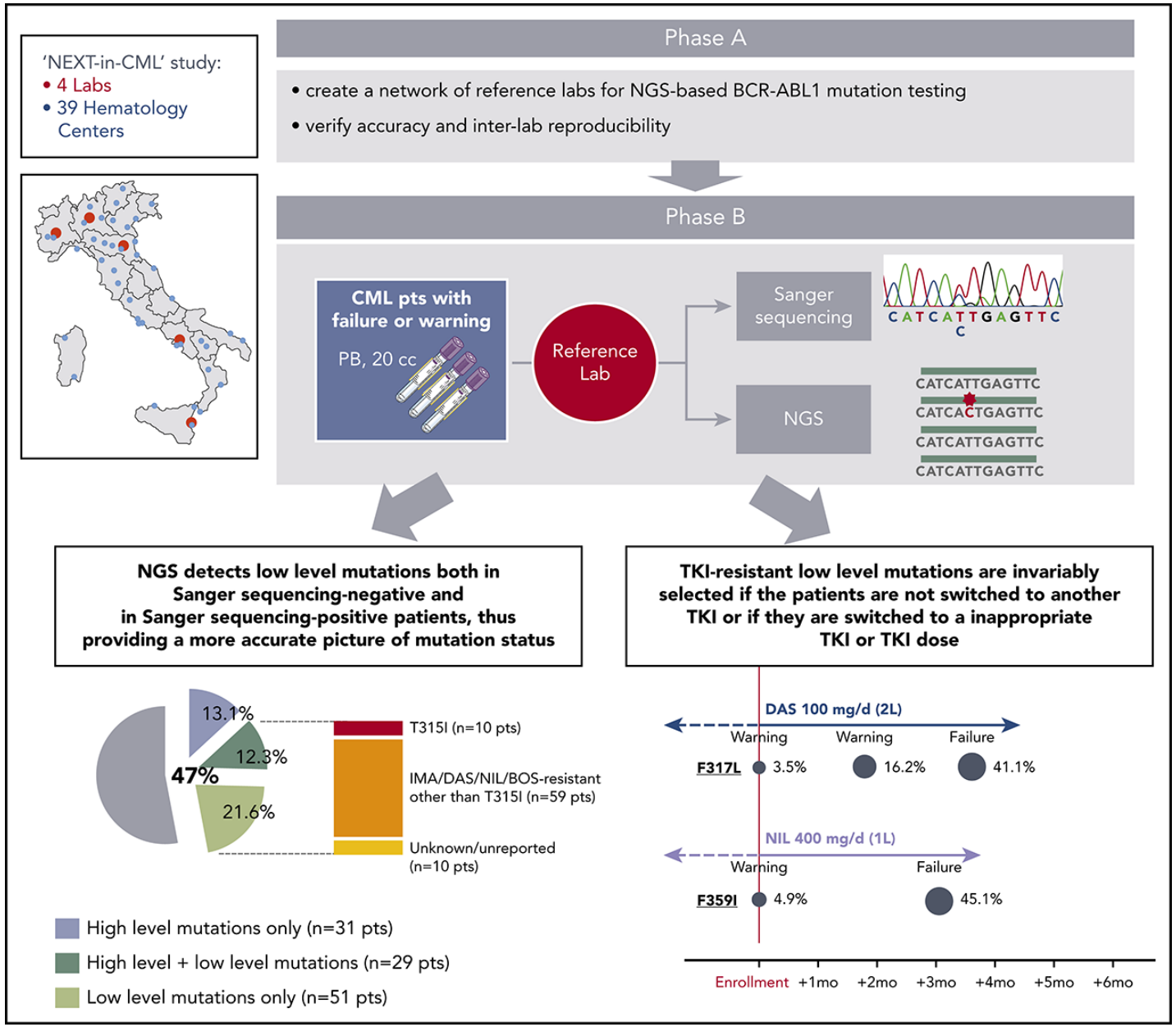
- Age ≥18 years.
- CP-CML. No prior history of AP-CML or BP-CML.
- On approved TKI therapy for at least 3 years.1,2
- Prior evidence of quantifiable BCR::ABL1 transcript.
- Stable molecular response (MR4; BCR::ABL1 ≤0.01% IS) for ≥2 years, as documented on at least 4 tests, performed at least 3 months apart.2
- Access to a reliable qPCR test with a sensitivity of detection of at least MR4.5 (BCR::ABL1 ≤0.0032% IS) and that provides results within 2 weeks.
- Monthly molecular monitoring for the first 6 months following discontinuation, bimonthly during months 7–12, and quarterly thereafter (indefinitely) for patients who remain in MMR (MR3; BCR::ABL1 ≤0.1% IS).
- Prompt resumption of TKI within 4 weeks of a loss of MMR with monthly molecular monitoring until MMR is re-established, then every 3 months thereafter is recommended indefinitely for patients who have reinitiated TKI therapy after a loss of MMR. For those who fail to achieve MMR after 3 months of TKI resumption, BCR::ABL1 kinase domain mutation testing should be performed, and monthly molecular monitoring should be continued for another 6 months.

[1] The feasibility of TFR following discontinuation of TKIs other than dasatinib, imatinib, or nilotinib has not yet been evaluated in clinical studies. It is reasonable to assume that the likelihood of TFR following discontinuation would be similar irrespective of TKI in patients who have achieved and maintained DMR (MR4.0; ≤0.01% *BCR::ABL1* IS) for ≥2 years, based on the extrapolation of findings from the studies that have evaluated TFR following discontinuation of imatinib, dasatinib, or nilotinib. [2] Data from the EURO-SKI study suggest that MR4.0 (*BCR::ABL1* ≤0.01% IS) for ≥3 years was the most significant predictor for successful discontinuation of imatinib.
Total duration of imatinib therapy for at least 6 years was also predictive of successful discontinuation (Saussele S, et al. Lancet Oncol 2018;19:747-757).

Requirements for TKI Discontinuation

Mandatory Requirements
• CML in first CP only
• Motivated patient with structured communication
• Access to high quality quantitative PCR*
• Patient's agreement to more frequent monitoring after stopping treatment.

Minimal Requirement (stop allowed)	Optimal Requirement (stop recommended for consideration)
• First-line therapy or second-line if intolerance was the only reason for changing TKI	
• Typical e13a2 or e14a2 *BCR::ABL1* transcripts	
• Duration of TKI therapy >5 years (>4 years for 2GTKI)	• Duration of TKI therapy >5 years
• Duration of DMR (MR^4 or better) >2 years	• Duration of DMR > 3 years if MR^4 • Duration of DMR > 2 years if $MR^{4.5}$
• No prior treatment failure	



NEXT-in-CML study

Taipei Veterans General Hospital Practice Guidelines Hematology

Chronic Lymphoid Leukemia

CLL/SLL staging system

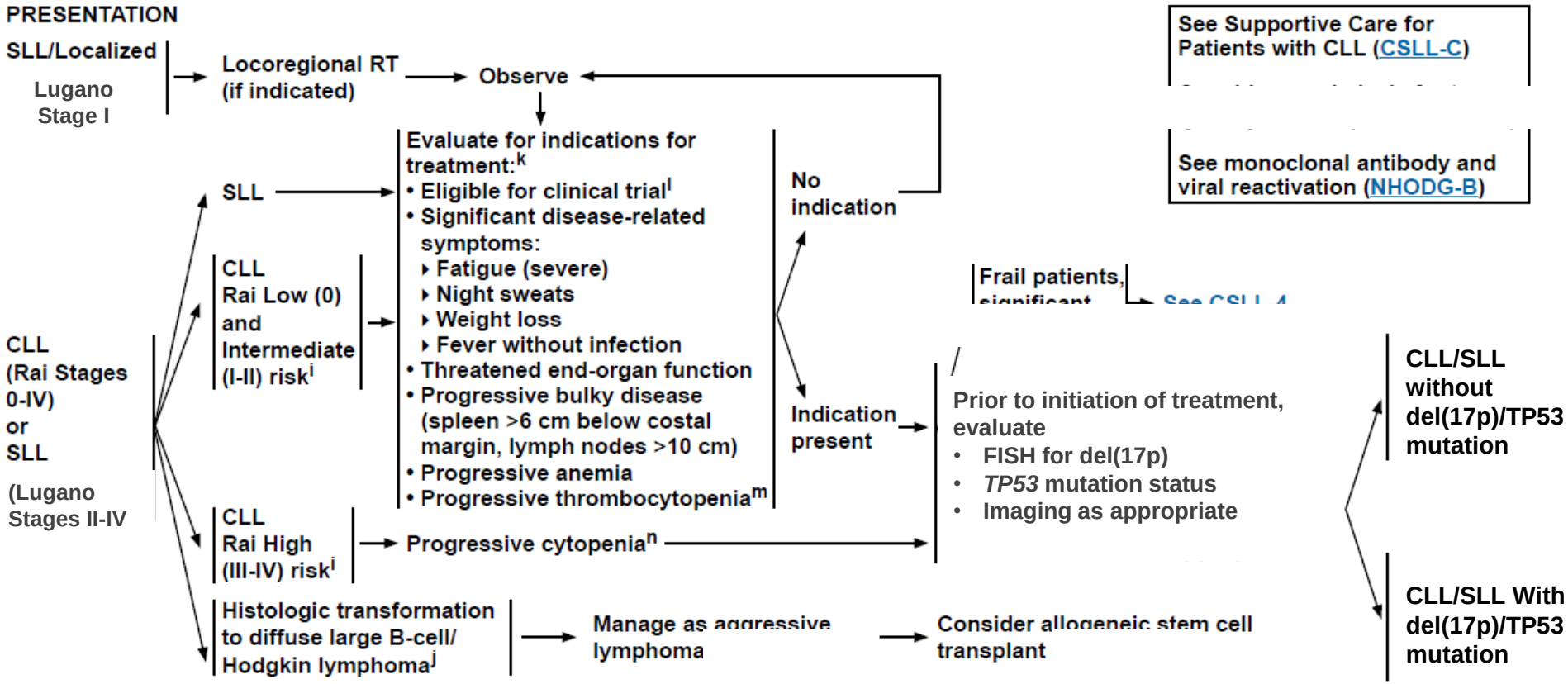
Rai System

Stage	Description	Risk Status
0	Lymphocytosis, lymphocytes in blood > 15,000/mcL and > 40% lymphocytes in the bone marrow	Low
I	Stage 0 with enlarged node(s)	Intermediate
II	Stage 0-I with splenomegaly, hepatomegaly, or both	Intermediate
III	Stage 0-II with hemoglobin < 11.0 g/dL or hematocrit < 33%	High
IV	Stage 0-III with platelets < 100,000/mcL	High

Binet System

Stage	Description
A	Hemoglobin ≥ 10 g/dL and Platelets ≥ 100,000/mm^3 and < 3 enlarged areas
B	Hemoglobin ≥ 10 g/dL and Platelets ≥ 100,000/mm^3 and ≥ 3 enlarged areas
C	Hemoglobin < 10 g/dL and/or Platelets < 100,000/mm^3 and any number of enlarged areas

CLL/SLL treatment algorithm



See CLL without del(11q) or de(17p)/TP53 mutation

CLL/SLL without del(17p)/*TP53* mutation (alphabetical by category)

FIRST-LINE THERAPY

Patients age ≥ 65 y OR patients < 65 y with significant comorbidities

- Acalabrutinib ± Obinutuzumab
- Venetoclax + Obinutuzumab
- Zanubrutinib
- Ibrutinib
- Bendamustine + anti-CD20 monoclonal antibody
- Obinutuzumab
- High-dose methylprednisolone (HDMP) + rituximab or obinutuzumab
- Chlorambucil

Patients age < 65 y without significant comorbidities

- Acalabrutinib ± Obinutuzumab
- Venetoclax + Obinutuzumab
- Zanubrutinib
- Ibrutinib
- Bendamustine + anti-CD20 monoclonal antibody
- FCR (fludarabine, cyclophosphamide, rituximab)
- Ibrutinib + obinutuzumab
- Ibrutinib + rituximab
- FR (fludarabine + rituximab)
- HDMP + rituximab or obinutuzumab

CLL/SLL without del(17p)/*TP53* mutation (alphabetical by category)

SECOND-LINE AND SUBSEQUENT THERAPY

Patients age ≥ 65 y OR patients < 65 y with significant comorbidities

- Acalabrutinib
- Zanubrutinib
- Ibrutinib
- Venetoclax + rituximab
- Chlorambucil + rituximab
- Lenalidomide ± rituximab
- Obinutuzumab
- Venetoclax
- Bendamustine + rituximab
- HDMP + rituximab or obinutuzumab
- Duvelisib
- Idelalisib ± rituximab

Patients age < 65 y without significant comorbidities

- Acalabrutinib
- Zanubrutinib
- Ibrutinib
- Venetoclax + rituximab
- Bendamustine + rituximab
- FCR
- Lenalidomide ± rituximab
- Obinutuzumab
- Venetoclax
- HDMP + rituximab or obinutuzumab
- Bendamustine, rituximab + ibrutinib
- Duvelisib
- Idelalisib ± rituximab

CLL/SLL with del(17p)/*TP53* mutation (alphabetical by category)

FIRST-LINE THERAPY

- Acalabrutinib ± Obinutuzumab
- Venetoclax + Obinutuzumab
- Zanubrutinib
- Ibrutinib
- FCR (for fit patients)
- Bendamustine + anti-CD20 monoclonal antibody
- HDMP + rituximab
- Obinutuzumab

SECOND-LINE AND SUBSEQUENT THERAPY

- Acalabrutinib
- Venetoclax + rituximab
- Venetoclax
- Zanubrutinib
- Ibrutinib
- HDMP + rituximab
- Lenalidomide ± rituximab
- Duvelisib
- Idelalisib ± rituximab