2010: AML Pre-HCT

The Acute Myelogenous Leukemia Pre-HCT Data Form is one of the Comprehensive Report Forms. This form captures AML-specific pre-HCT data such as: the recipient's hematologic and cytogenetic findings at the time of diagnosis and prior to the start of the preparative regimen, pre-HCT treatments administered, and disease status prior to the preparative regimen.

This form must be completed for all recipients randomized to the Comprehensive Report Form (CRF) track whose primary disease is reported on Pre-TED Disease Classification Form (Form 2402) as Acute Myelogenous Leukemia (AML or ANLL) or Other Acute Leukemia (OAL). Additional disease insert forms will be required if the recipient had Myelodysplastic/Myeloproliferative Syndrome (MDS/MPS), Aplastic Anemia, or Juvenile Myelomonocytic Leukemia (JMML) prior to their diagnosis of Acute Myelogenous Leukemia.

Subsequent Transplant

If this is a report of a second or subsequent transplant for the same disease subtype and **this baseline disease insert was not completed for the previous transplant** (e.g., patient was on TED track for the prior HCT, prior HCT was autologous with no consent, etc.), begin at question 1.

If this is a report of a second or subsequent transplant for a **different disease** (e.g., patient was previously transplanted for a disease other than Acute Myelogenous Leukemia), begin at question 1.

If this is a report of a second or subsequent transplant for the **same disease and this baseline disease insert has previously been completed**, check the indicator box and continue with question 127.

Manual Updates:
Sections of the Forms Instruction Manual are frequently updated. In addition to documenting the changes within each manual section, the most recent updates to the manual can be found below. For additional information, select the manual section and review the updated text.

If you need to reference the historical Manual Change History for this form, please click here or reference the retired manual section on the Retired Forms Manuals webpage.

Date	Manual Section	Add/ Remove/ Modify	Description
2/ 24/ 17	Comprehensive Disease-Specific Manuals	Modify	Updated explanations of triggers for disease inserts to refer to the primary disease reported on the Pre-TED Disease Classification Form (Form 2402) instead of the Pre-TED Form (Form 2400)
12/ 3/15	2010: AML Pre-HCT	Modify	Updated text in question 12: If the patient is suspected to have had a preceding hematologic disorder, but it was not definitively documented or diagnosed, indicate “suspected” and continue with question ~~16.~~ *14.*

Q1-18: Disease Assessment at Diagnosis

Question 1: What was the date of diagnosis?

Report the date of the first pathological diagnosis (e.g., bone marrow biopsy, extramedullary mass biopsy) of AML. Enter the date the sample was collected for examination. If the diagnosis was determined at an outside center and no documentation of a pathological or laboratory assessment is available, the dictated date of diagnosis within a physician note may be reported. Do not report the date symptoms first appeared. The date of diagnosis is important because the interval between diagnosis and HCT is often a significant indicator for the recipient's prognosis post-HCT.

If the exact pathological diagnosis date is not known, use the process for reporting partial or unknown dates as described in General Instructions, Guidelines for Completing Forms.

Question 2: Is the disease (AML) therapy-related? (not MDS/MPN)

Agents such as radiation or systemic therapy used to treat other diseases (e.g., Hodgkin lymphoma, non-Hodgkin lymphoma, and breast cancer) can damage the marrow and lead to a secondary malignancy such as AML. If the diagnosis of AML is therapy-related, check "yes" and continue with question 3.

If the diagnosis of AML is not therapy-related, check "no" and continue with question 11.

- If AML was preceded by therapy-related MDS, check "no."
- If the recipient developed AML after an environmental exposure (e.g., exposure to benzene), check "no."

If it is unknown whether or not the diagnosis of AML was therapy-related, check "unknown" and continue with question 11.

Questions 3-4: Specify prior disease.

Indicate the recipient's primary disease before the diagnosis of therapy-related AML. If the patient's prior disease is best classified as "other disease (malignant or non-malignant)," specify in question 4.

Questions 5-6: Date of diagnosis of prior disease.

Specify if the date of diagnosis of the prior disease is "known" or "unknown." If the date is "known," continue with question 6 and report the date of the first pathological diagnosis (e.g., bone marrow or tissue biopsy) of

the prior disease. Enter the date the sample was collected for examination. Do not report the date symptoms first appeared. This date must be prior to the AML diagnosis date entered in question 1.

If the date is “unknown,” continue with question 7.

Questions 7-10: Specify therapy for prior disease.

Systemic therapy refers to a delivery mechanism where a therapeutic agent is delivered orally or intravenously, enters the bloodstream, and is distributed throughout the body. Systemic therapy in the setting of malignancy generally refers to chemotherapy or cytotoxic therapy. Intrathecal therapy is administered into the lumbar cerebral spinal fluid and acts on the central nervous system. Radiation therapy uses high-energy, ionizing radiation to kill malignant cells. It is typically referred to as radiation therapy, x-ray therapy (XRT), or radiotherapy.

For each listed treatment, indicate “yes,” “no,” or “unknown.” If the treatment administered was “other treatment,” specify the type of treatment given in question 10. Check all that apply; do not leave any response blank.

Question 11: Did the recipient have an antecedent hematologic disorder (preleukemia or myelodysplastic syndrome)?

AML may evolve from MDS or MPS. This transformation is typically distinguished by the percentage of blasts in the bone marrow. AML that transforms from MDS or MPS has a poorer survival prognosis because of the association with unfavorable chromosomal abnormalities.

AML can also evolve from Juvenile Myelomonocytic Leukemia (JMML). JMML is a rare form of chronic leukemia that affects young children, usually before the age of five. JMML results from DNA mutations in white blood cells called monocytes. Normal monocytes attack invading microorganisms and assist lymphocytes in carrying out immune functions. Abnormal monocytes in JMML accumulate in the bone marrow and interfere with the production of normal white blood cells, red blood cells, and platelets.

Additionally, aplastic anemia may progress to MDS and/or AML. Aplastic anemia is a broad classification that refers to bone marrow failure characterized by pancytopenia and marrow hypoplasia.

If there is documentation of a diagnosed or suspected antecedent (prior) hematologic disorder or a concurrently diagnosed hematologic disorder, check “yes” and continue with question 12.

If the recipient did not have a documented or suspected antecedent hematologic disorder or concurrent diagnosis of another hematologic disorder, check “no” and continue with question 16.

If it is unknown whether the recipient had a documented or suspected antecedent hematologic disorder, check “unknown” and continue with question 16.

Question 12: Specify if the antecedent hematologic disorder was:

If the patient’s other hematologic disorder diagnosis preceded their AML diagnosis indicate “documented” and continue with question 13.

If the other hematologic disorder was diagnosed on the same evaluation that resulted in AML diagnosis, indicate “concurrent” diagnosis and continue with question 13.

If the patient is suspected to have had a preceding hematologic disorder, but it was not definitively documented or diagnosed, indicate “suspected” and continue with question 16.

Question 13: What was the date of diagnosis of antecedent hematologic disorder?

Report the date of the first pathological diagnosis (e.g., bone marrow or tissue biopsy) of the antecedent hematologic disorder. Enter the date the sample was collected for examination. Do not report the date symptoms first appeared. This date must be prior to the AML diagnosis date entered in question 1 for documented antecedent hematologic disorders; however, this date should be the same as the AML diagnosis date entered in question 1 for concurrently diagnosed hematologic disorders.

Example 1: Patient presents with fatigue; initial work-up reveals anemia. Subsequent bone marrow biopsy with specimen taken on May 14 shows MDS, refractory anemia with excess blasts at 7%, or RAEB-1. The patient chooses supportive therapy and their disease progresses to AML, which is shown in a bone marrow biopsy with 28% blasts on September 7 of the same year. This patient had a known antecedent hematologic disorder. May 14 would be reported as the date of diagnosis of antecedent hematologic disorder, which was RAEB-1 (reported in question 13). The diagnosis date of AML (question 1) would be reported as September 7.

Example 2: Patient presents with severe fatigue and chronic upper respiratory infections; initial work-up reveals anemia. Subsequent bone marrow biopsy with specimen taken June 17 shows 26% blasts and myelodysplasia-related features; an aspirate sample was sent for cytogenetic testing, which reveals monosomy 7. The physician states that this patient has AML arising from MDS. Report that the patient had a concurrent hematologic disorder. June 17 would be reported as the date of antecedent hematologic disorder (question 13) and the diagnosis date of AML (question 1).

Question 14-15: What was the classification of the hematologic disorder at diagnosis?

Indicate the classification of the antecedent hematologic disorder at diagnosis. Do not report any transformations or progressions of an antecedent hematologic disorder. For example: a patient is diagnosed

with RAEB-1, which progresses to RAEB-2 prior to transformation to AML; report “RAEB-1” as the antecedent hematologic disorder.

Report myelodysplastic syndrome that has not been classified as “Myelodysplastic syndrome, unclassifiable.”

For a list of MDS/MPN subtypes and their diagnostic criteria, see Appendix H.

Question 16: Did the recipient have a predisposing condition prior to the diagnosis of AML?

A predisposing condition is a condition that contributes to the susceptibility of developing leukemia. Therefore, diagnosis of the condition increases the likelihood that the recipient will develop leukemia. If the recipient has a documented history of a predisposing condition, check “yes” and continue with question 17. If there is no history of a predisposing condition or predisposition is unknown, indicate “no” or “unknown” and continue with question 19.

Questions 17-18: Specify condition.

Bloom syndrome is an autosomal recessive genetic disorder characterized by excessive chromosome breakage and corresponding rearrangements, proportional dwarfism, and sun sensitivity. The chromosomal instability seen in Bloom syndrome is generally assumed to be responsible for these individuals’ predisposition to malignancy.

Down syndrome is also a chromosomal disorder (trisomy 21). It is characterized by an additional chromosome 21. Down syndrome patients exhibit a particular set of facial characteristics, growth deficiency, and cognitive impairment. Although Down syndrome patients have a reduced risk of developing many common malignancies, they have an increased risk of developing leukemia.

Fanconi anemia is a rare genetic blood disorder that prevents the body from producing a sufficient number of new blood cells to function properly. Abnormal blood cells may also be produced. These patients are short in stature, exhibit skeletal anomalies, and have an increased risk of developing solid tumors and leukemias.

Neurofibromatosis type 1, also known as von Recklinghausen disease, is an autosomal dominant genetic disorder characterized by mutation of chromosome 17 resulting in the inactivation of the NF1 gene. This results in abnormal growth and proliferation of neural crest cells. Patients with neurofibromatosis type 1 often have multiple neurofibromas (benign neural tumors), skeletal abnormalities, café au lait spots, lisch nodules, freckling in the axilla or groin, and/or optic nerve glioma. Patients with biallelic inactivation of NF1 may have an increased risk of developing malignant neoplasms, including rhabdomyosarcoma, pheochromocytoma, and, in children, myelodysplastic syndrome and acute leukemia.

Indicate the recipient's predisposing condition prior to the diagnosis of leukemia. If AML arose from aplastic anemia or Fanconi anemia, also complete the associated baseline disease inserts (CIBMTR forms 2028 and 2029, respectively). If the condition was "other," specify the condition in question 18.

Q19-87: Laboratory Studies at Diagnosis

Report findings at the time of diagnosis; if multiple studies were performed prior to the institution of therapy, report the latest values prior to the start of treatment.

Questions 19-21: WBC

Indicate whether the white blood count (WBC) was “known” or “unknown” at the time of AML diagnosis. If “known,” report the laboratory count and unit of measure documented on the laboratory report in question 20; indicate the date sample was collected in question 21. If “unknown,” continue with question 22.

Questions 22-24: Blasts in blood

Indicate whether the percentage of blasts in the peripheral blood was “known” or “unknown” at the time of AML diagnosis. If “known,” report the percentage documented on the laboratory report in question 23; indicate the date sample was collected in question 24. If “unknown,” continue with question 25.

✻ If a differential was performed and there were no blasts present in the peripheral blood, the laboratory report may not display a column for blasts. In this case, it can be assumed that no blasts were present and “0” can be entered on the form.

! Blast counts obtained by flow cytometry should be reflected under the flow cytometry data fields; only report percentage blasts as determined by peripheral blood differential.

Questions 25-27: Blasts in bone marrow

Indicate whether the percentage of blasts in the bone marrow was “known” or “unknown” at the time of AML diagnosis. If “known,” report the percentage documented on the laboratory report in question 26; indicate the date sample was collected in question 27. If “unknown,” continue with question 28.

✻ If the bone marrow pathology report states a range for blasts, enter the average of the range rounded to the nearest whole number (e.g., if 0-5%, enter 3%).
If the report indicates “sheets of blasts” or “packed marrow,” report 100%.
If the report states > n% blasts, enter (n+1)% on the form. For example, if the laboratory report indicates > 90% blasts, report 91%.
If the report states <n% blasts, enter (n-1)% on the form. For example, if the laboratory report indicates <5% blasts, report 4%.

Question 28: Was extramedullary disease present?

Extramedullary refers to disease found in organs or tissue outside the bone marrow or blood stream (e.g., central nervous system, testes, skin, soft tissue, etc.). Examples of extramedullary disease in AML patients include granulocytic sarcoma, subcutaneous nodules, leukemia cutis, and meningeal leukemia. If there is evidence of extramedullary disease at the time of diagnosis, indicate “yes” and continue with question 29. If there is no evidence of extramedullary disease at the time of diagnosis, indicate “no” and continue with question 36. If the status of extramedullary sites at the time of diagnosis is unknown, indicate “unknown” and continue with question 36.

Questions 29-35: Specify site(s) of extramedullary disease.

Indicate all sites of extramedullary disease. If question 28 was answered “yes,” then each of questions 29-34 must be answered as “yes” or “no.” If question 34, “other” site of extramedullary disease is answered “yes,” specify site in question 35.

Question 36: Were cytogenetics tested (conventional or FISH)?

Cytogenetic analysis is the study of chromosomes. Cytogenetic assessment involves testing blood or bone marrow for the presence of a known chromosomal abnormality that reflects the recipient’s disease. Testing methods you may see include conventional chromosome analysis (karyotyping), fluorescence in situ hybridization (FISH), or microarray comparative genomic hybridization (aCGH) testing. For more information about cytogenetic testing and terminology, see Appendix C.

Table 1. Examples of AML Cytogenetic Findings Categorized by Prognosis

Favorable	Intermediate	Poor
t(15;17) t(8;21) inv(16) or t(16;16)	Normal +8 t(9;11) *All other abnormalities*	≥ 3 abnormalities 5- or 5q- 7- or 7q- t(9;22)

Indicate if cytogenetic studies were obtained at the time the recipient was diagnosed with AML or prior to the start of treatment.

If cytogenetic studies were obtained, check “yes” and continue with question 37.

If cytogenetic studies were not obtained or it is unknown if chromosome studies were performed, indicate “no” or “unknown” and continue with question 76.

Question 37: Date sample collected

Report the date the sample was collected for cytogenetic or FISH testing. If multiple studies were performed prior to the start of therapy, report the latest assessment prior to the start of treatment.

If the exact date is not known, use the process for reporting partial or unknown dates as described in General Instructions, Guidelines for Completing Forms.

Question 38: Results of test

If cytogenetic studies identified abnormalities (any karyotype other than 46XX or 46XY), indicate "abnormalities identified" and continue with question 39.

If cytogenetic studies yielded no evaluable metaphases or there were no abnormalities identified, indicate such and continue with question 76.

Questions 39-74: Specify abnormalities

If question 38 indicates that abnormalities were identified, each of questions 39-73 must be answered as "yes" or "no." Do not leave any response blank. Indicate "yes" for each cytogenetic abnormality identified at diagnosis or prior to the start of first therapy; indicate "no" for all options not identified on cytogenetic assessment at diagnosis or prior to the start of first therapy. If one or more abnormalities are best classified as "other abnormality," specify in question 74.

If ≥ 3 cytogenetic abnormalities were identified at the time of AML diagnosis or prior to the start of first therapy, select "yes" for question 72 (complex, ≥ 3 distinct abnormalities) and specify the corresponding abnormalities in questions 39-71. If any of these abnormalities are not listed among 39-71, report "other abnormality," and specify in question 74. For example, if the karyotype included -7, +8, and -13, report "yes" for questions 40, 46, 72, and 73/74. Complete the remaining indicators as "no," and do not leave any response blank.

Question 75: Was documentation submitted to the CIBMTR (e.g., cytogenetic or FISH report)?

Indicate if a copy of the cytogenetic or FISH report is attached. Use the Log of Appended Documents (Form 2800) to attach a copy of the cytogenetic or FISH report. Attaching a copy of the report may prevent additional queries.

Question 76: Were tests for molecular markers performed (e.g., PCR)?

Molecular assessment involves testing blood or bone marrow for the presence of known molecular markers associated with the recipient's disease. Molecular assessments are the most sensitive test for genetic

abnormalities and involve amplifying regions of cellular DNA by polymerase chain reaction (PCR), typically utilizing RNA to generate complementary DNA through reverse transcription (RT-PCR).

Indicate if molecular studies were obtained at the time the recipient was diagnosed with AML or prior to the start of treatment.

If molecular studies were obtained, check “yes” and continue with question 77.

If molecular studies were not obtained or it is unknown if molecular studies were performed, indicate “no” or “unknown” and continue with question 88.

Question 77: Date sample collected

Report the date the sample was collected for molecular testing.

If the exact date is not known, use the process for reporting partial or unknown dates as described in General Instructions, Guidelines for Completing Forms.

Questions 78-86: Specify abnormalities.

If question 76 indicates that molecular markers were identified, then each of questions 78-85 must be answered as “positive,” “negative,” or “not done.” Do not leave any response blank. If question 85 is answered “positive,” specify the identified molecular marker in question 86. Duplicate questions 85-86 if more than one “other molecular marker” is identified.

Table 2. Common Molecular Markers Associated with AML

Molecular Abnormality	Characteristics
CEBPA	CEBPA, *aka* CCAAT/enhancer binding protein α, is a transcription factor required for the differentiation of granulocytes. Numerous CEBPA mutations have been identified in relation to AML, with the majority of patients displaying biallelic mutations ultimately resulting in the down regulation of gene activity. Decreased gene activity results in decreased differentiation potential for immature granulocytes. An estimated 7-15% of AML patients have CEBPA mutations and CEBPA mutations are generally found in M1 and M2 subtypes in conjunction with intermediate-risk cytogenetics. Studies show an association with more favorable outcomes.[1]
FLT3-D835 point mutation	FLT3 encodes a receptor tyrosine kinase. The FLT3-D835 point mutation, *aka* FLT3-TKD, is an activating mutation impacting tyrosine-kinase domains. FLT3 mutations are found in up to 1/3 of all AML patients. The clinical significance of TKD activation remains unclear. FLT3-D385 mutations are often found in conjunction with other mutations. Overall, FLT3-D385 is not considered a favorable or poor prognostic indicator. However, in certain combinations with other mutations, there are associations with both improved and diminished survival.[23]

FLT3-ITD mutation	FLT3 encodes a receptor tyrosine kinase. The FLT3-ITD (internal tandem duplication) interferes with certain down regulation functions within receptor tyrosine kinases, leading to activation of TK activity. FLT3 mutations are found in up to 1/3 of all AML patients. FLT3-ITD is considered a poor prognostic factor. Sorafenib (Nexavar) has been shown to initially improve disease response in FLT3-ITD-positive AML.[4]
IDH1	Isocitrate Dehydrogenase (IDH) is an oxidative enzyme involved in the citric acid cycle. IDH1 mutations result in incorrect catalytic activity, leading to increased levels of an oncometabolite, 2-hydroxyglutarate. The pathologic activity of IDH1 mutations is still being studied, but it has been suggested that IDH mutations may be a distinct mechanism in AML pathogenesis; research models show they may cause an accumulation of hematopoietic progenitor cells. Early research suggests IDH1 mutation may be a less favorable prognostic indicator.[5]
IDH2	Isocitrate Dehydrogenase (IDH) is an oxidative enzyme involved in the citric acid cycle. IDH2 is a mitochondrial homolog to IDH1. Much like IDH1 mutations, IDH2 mutations result in incorrect catalytic activity, leading to increased levels of (D)-2-hydroxyglutarate. The pathologic activity of IDH2 mutations are still being studied, but it has been suggested that IDH mutations may be a distinct mechanism in AML pathogenesis; research models show they may cause an accumulation of hematopoietic progenitor cells. Early research suggests IDH2 mutation may be a more favorable prognostic indicator, unlike IDH1 mutation, though there may be differences based on where the IDH2 mutation occurs in gene.[6]
KIT	KIT encodes a receptor tyrosine kinase. The KIT mutations at exons 8 and 17 are associated with activation of encoded proteins, resulting in activation impacting tyrosine-kinase domains. Patients with t(8;21) and inv(16) cytogenetics are frequently screened for KIT mutations, which adversely affect prognosis in these patients.[7]
NPM1	NPM1 encodes a protein responsible for multiple cellular functions, including the regulation of the ARF-p53 tumor suppressor pathway. Mutations in NPM1 result in gene over-expression and subsequent inactivation of ARF-p53 tumor suppression pathway. NPM1 mutations are one of the most common molecular markers seen in AML and are associated with improved survival.[8]
Other molecular marker	Assessments for other molecular markers known or believed to be associated with AML may be performed. If these studies are performed, indicate “yes” and specify in question 86.

[1] Lin L, Chen C, Lin D, Tsay W, Tang J, Yeh Y, Shen H, Su F, Yao M, Huang S, Tien H. (2005). Characterization of CEBPA Mutations in Acute Myeloid Leukemia: Most patients with CEBPA mutations have biallelic mutations and show a distinct immunophenotype of the leukemic cells. *Clin Cancer Res*, 11, 1372-9.

[2] Mead AJ, Linch DC, Hills RK, Wheatley K, Burnett AK, Gale RE. (2007). FLT3 tyrosine kinase domain mutations are biologically distinct from and have a significantly more favorable prognosis than FLT3 international tandem duplications in patient with acute myeloid leukemia. *Blood*, 110, 1262-70.

[3] Whitman SP, Ruppert AS, Radmacher, MD, et al. (2008). FLT3 D835/I836 mutations are associated with poor disease-free survival and a distinct gene-expression signature among younger adults with de novo cytogenetically normal acute myeloid leukemia lacking FLT3 internal tandem duplications. *Blood*, 111, 1552-59.

[4] Man CH, Fung TK, Ho C, et al. (2011). Sorafenib treatment of FLT-ITD+ acute myeloid leukemia: favorable initial outcome and mechanisms of subsequent non-responsiveness associated with the emergence of a D835 mutation. *Blood*, 119 (22), 5133-43.

[5] Marucci G, Maharry K, Wu YZ, et al. (2010). *IDH1* and *IDH2* Gene Mutations Identify Novel Molecular Subsets Within De Novo Cytogenetically Normal Acute Myeloid Leukemia: A Cancer and Leukemia Group B Study. J *Clin Oncol*, 28(14), 2348-55.

[6] Green CL, Evans CM, Zhao L, et al. (2011).The prognostic significance of IDH2 mutations in AML depends on the location of the mutation. *Blood*, 118(2), 409-12.

[7] Döhner K, Döhner H. (2008).Molecular characterization of acute myeloid leukemia. *Haematologica*, 93(7), 976-82.

[8] Varhaak RGW, Goudswaard CS, van Putten W, et al. (2005).Mutations in nucleophosmin (NPM1) in acute myeloid leukemia (AML): association with other gene abnormalities and previously established gene expression signatures and their favorable prognostic significance. *Blood*, 106(12), 3747-54.

Question 87: Was documentation submitted to the CIBMTR?

Indicate if a copy of the molecular report(s) is attached. Use the Log of Appended Documents (Form 2800) to attach a copy of the molecular report. Attaching a copy of the report may prevent additional queries.

Q88-126: Pre-HCT Therapy

Complete a “Line of Therapy” section for each line of therapy administered prior to the start of the preparative regimen. If multiple lines of therapy were administered, copy and complete questions 89-125 for each line of therapy.

Question 88: Was therapy given?

Indicate if the recipient received treatment for AML after the time of diagnosis and before the start of the preparative regimen. If “yes,” continue with question 89. If “no”, continue with question 126. For recipients with MDS that transformed to AML, only report therapy given after the transformation to AML; any treatments given prior to the transformation would be reported on the MDS Pre-HCT Data form (Form 2014).

Question 89: Purpose of therapy

Indicate the purpose of the therapy administered between the time of AML diagnosis and the start of the preparative regimen.

Chemotherapy is initially given as induction therapy intended to bring the disease into remission. Recipients usually have one to two cycles of induction therapy; disease prognosis is considered less favorable if the patient fails to achieve remission with first induction therapy and is even poorer in patients failing two or more induction therapies.[1] An example of a common induction therapy for all AML subtypes except M3 is a combination of an anthracycline and cytarabine, commonly known as “7+3.” In this regimen, cytarabine is typically administered for seven days at a dose of 100 mg/m2/day. The anthracycline (usually daunorubicin at 45 to 60 mg/m2/day or idarubicin at 12 mg/m2/day) is generally given on the first three days the cytarabine is given.

The second phase of chemotherapy is known as consolidation therapy. The goal of consolidation therapy is to destroy any remaining leukemia cells and sustain remission. An example of a common consolidation therapy for all AML subtypes except M3 is high-dose cytarabine, commonly referred to as “HiDAC.” In this regimen, cytarabine is typically administered at a dose exceeding 10 g/m2 per cycle.

Maintenance chemotherapy may follow consolidation therapy; maintenance chemotherapy is given in lower doses and is intended to prolong a remission. Maintenance therapy is used less commonly for the treatment of AML than other malignancies. Treatment may also be administered for relapsed disease. Much like induction therapy, treatment for relapse is intended to bring the disease back into remission. Systemic therapeutic agents used to induce remission following relapse often differ from those used in the initial induction, since the disease is often resistant to many of the agents used earlier in the disease course and

is considered high-risk with a poor prognosis. Allogeneic HCT is often considered the only potential "cure" for relapsed disease.

[1] Ravandi F, Cortes J, Faderl S, O'Brien S, Garcia-Manero G, Verstovesek S, Santos F, Shan J, Brandt M, de Lima M, Pierce S, Kantarjian H. (2010). Characteristics and outcome of patients with acute myeloid leukemia refractory to one cycle of high-dose cytarabine-based induction therapy. *Blood*, 116(26), 5818-23.

Question 90: Systemic therapy

Systemic therapy refers to a delivery mechanism where a therapeutic agent is delivered orally or intravenously, enters the bloodstream, and is distributed throughout the body. Intrathecal therapy is administered via injection into the subarachnoid space; these drugs reach the cerebral spinal fluid and act on the central nervous system.

Indicate "yes" if the patient received systemic or intrathecal therapy and continue with question 91.
If the patient did not receive systemic or intrathecal therapy, indicate "no" and continue with question 114.

Questions 91-92: Date therapy started

Indicate "known" if the therapy start date is documented and specify the date systemic therapy was first administered in question 92. If the date is unknown, indicate such and continue with question 93.

Questions 93-94: Date therapy stopped

Indicate "known" if the therapy completion date is documented and specify the date the therapy stopped in question 94. If the patient is receiving systemic therapy in cycles, specify the first day of the last cycle of systemic therapy. If the patient is receiving a single line or single administration, indicate the last day systemic therapy was administered.

If the date is unknown, indicate such and continue with question 95.

Questions 95-96: Number of cycles

Indicate if the number of cycles is "known" or "unknown." If the number of cycles is known, continue with question 96 and specify the number of cycles of chemotherapy administered. If the patient is receiving a single administration or one line of chemotherapy, indicate a single cycle.

If the number of cycles is unknown, continue with question 97.

Questions 97-113: Specify systemic or intrathecal therapy agents

Systemic therapy agents and treatment regimens vary based on disease, prognosis, and protocol. Drugs may be administered in an inpatient or outpatient setting, and treatment may consist of one or multiple drugs. Additionally, drugs may be administered on a single day, over consecutive days, or continuously.

Indicate “yes” or “no” for each chemotherapy drug listed. Do not leave any response blank. If the recipient received a chemotherapy agent that is not listed, check “yes” for “other systemic therapy” and specify the treatment in question 113.

Reporting Cytarabine doses (Questions 101 & 102)
In some cases the dose of cytarabine administered for treatment may not be available. Generally, low- to intermediate-dose Ara-C is considered ≤ 10 g/m2/cycle, as is commonly seen in standard “7+3” induction. High dose Ara-C is considered > 10 g/m2/cycle, as is commonly seen in “HiDAC” therapy.

Reporting Intrathecal Therapy (Question 108)
Any intrathecal therapy administered as part of a pre-HCT line of therapy should be reported only in the “intrathecal therapy” category (question 108) and not in its corresponding drug category. For example, if intrathecal cytarabine is administered as part of a pre-HCT line of therapy and the patient does not receive systemic cytarabine, questions 101-102 are answered “no”, and question 108 is answered “yes.” It is not necessary to specify the intrathecal agent in question 113.

Question 114: Radiation therapy

Radiation therapy uses high-energy, ionizing radiation to kill malignant cells. However, much like non-targeted systemic therapy, radiation therapy does not specifically target malignant cells and does have significant side effects. For that reason, high-dose radiation often targets a limited field. Radiation therapy is not typically used in the treatment of AML and is generally reserved for the treatment of brain, spinal fluid, or testicular involvement.

Indicate if the recipient received radiation treatment for AML after the time of diagnosis and before the start of the preparative regimen. If “yes,” continue with question 115. If “no”, continue with question 122.

Question 115: Date therapy started

Indicate “known” if the radiation therapy start date is documented, continue with question 116 and specify the first date of radiation administration. If the date is unknown, indicate such and continue with question 117.

Question 117: Date therapy stopped

Indicate “known” if the radiation therapy completion date is documented, continue with question 118 and specify the last date of radiation administration. If the date is unknown, indicate such and continue with question 119.

Questions 119-121: Specify site(s) of radiation therapy

Indicate “yes” or “no” for each radiation site. Do not leave any response blank. Question 119 asks if radiation was delivered to the central nervous system; the central nervous system consists of the brain and spinal cord. If the recipient received radiation to any other site, indicate “yes” for question 120 and specify the site in question 121.

Question 122: Best Response to Line of Therapy

Complete hematologic response (CR) is a treatment response where all of the following criteria are met for at least four weeks:

- < 5% blasts in the bone marrow
- Normal maturation of all cellular components in the bone marrow
- No blasts with Auer rods
- No extramedullary disease (e.g., central nervous system or soft tissue involvement)
- ANC of > 1,000/µL
- Platelets ≥ 100,000/µL
- Transfusion independent

Include recipients with persistent cytogenetic or molecular testing abnormalities who otherwise meet all criteria of hematologic CR. Recipients with persisting extramedullary disease are not considered to be in CR.

Indicate if the patient’s best response to this line of therapy was a complete remission or was not a complete remission.

Question 123: Date assessed

Enter the date the best response to the line of therapy was established. Report the date of the pathological evaluation (e.g., bone marrow biopsy); if no pathologic evaluation was reported, report the date of blood/serum assessment (e.g., CBC, peripheral blood smear). Enter the date the sample was collected for pathological and/or laboratory evaluation. If the recipient was treated for extramedullary disease and a radiological assessment (e.g., X-ray, CT scan, MRI scan, PET scan) was performed to assess disease

response, enter the date the imaging took place. If no pathological, radiographic, or laboratory assessments were performed to establish the best response to the line of therapy, report the office visit in which the physician clinically assessed the recipient's response.

If the exact date is not known, use the process for reporting partial or unknown dates as described in General Instructions, Guidelines for Completing Forms.

Question 124: Did the recipient relapse following this line of therapy?

Relapse is the recurrence of disease after CR. AML relapse is demonstrated by one or more of the following findings:

- 5% blasts in the marrow and/or peripheral blood
- Extramedullary disease evident upon radiographic examination
- Disease presence determined by a physician upon clinical assessment

Indicate if relapse occurred following the line of therapy being reported.

Question 125: Date of relapse

Enter the date that relapse was established following the line of therapy. If reporting a pathological evaluation (e.g., bone marrow) or blood/serum assessment (e.g., CBC, peripheral blood smear), enter the date the sample was collected. If extramedullary disease was detected upon radiographic examination (e.g., X-ray, CT scan, MRI scan, PET scan), enter the date the imaging took place. If the physician determines evidence of relapse following a clinical assessment during an office visit, report the date of assessment.

If the exact date is not known, use the process for reporting partial or unknown dates as described in General Instructions, Guidelines for Completing Forms.

Question 126: Did the recipient have central nervous system leukemia at any time prior to the start of the preparative regimen?

Central nervous system leukemia is a disease of the leptomeninges, membranes that surround the brain and spinal cord. Indicate if the recipient had central nervous system involvement by AML at any time between the AML diagnosis and prior to the start of the preparative regimen. In the absence of a negative CSF assessment, lack of neurological signs and symptoms documented throughout the patient's disease course is sufficient to indicate that the recipient never had central nervous system leukemia. If the patient's CNS status was unknown at any time prior to the start of the preparative regimen, indicate "unknown." If the patient never had a CNS evaluation (e.g., CSF) and it is not clear that the patient never had neurological signs and symptoms, indicate "unknown."

Q127-192: Laboratory Studies at Last Evaluation Prior to the Start of the Preparative Regimen

These questions are intended to determine the hematological status of the recipient prior to the preparative regimen. Testing may be performed multiple times within the pre-transplant work-up period (approximately 30 days) prior to the start of the preparative regimen; report the most recent laboratory values. Laboratory values obtained on the first day of the preparative regimen may be reported as long as the sample was drawn before any radiation or systemic therapy was administered.

Questions 127-129: WBC

Indicate whether the white blood count (WBC) was “known” or “unknown” immediately prior to the start of the preparative regimen. If “known,” report the laboratory count and unit of measure documented on the laboratory report in question 128; indicate the date the sample was collected in question 129. If “unknown,” continue with question 130.

Questions 130-132: Blasts in blood

Indicate whether the percentage of blasts in the peripheral blood was “known” or “unknown” immediately prior to the start of the preparative regimen. If “known,” report the percentage documented on the laboratory report in question 131; indicate the date the sample was collected in question 132. If “unknown,” continue with question 133.

> ✻ If a differential was performed and there were no blasts present in the peripheral blood, the laboratory report may not display a column for blasts. In this case, it can be assumed that no blasts were present and “0” can be entered on the form. Blasts quantified in the peripheral blood by flow cytometry are captured separately in question 187.

Questions 133-135: Blasts in bone marrow

Indicate whether the percentage of blasts in the bone marrow was “known” or “unknown” immediately prior to the start of the preparative regimen. If “known,” report the percentage documented on the laboratory report in question 134; indicate the date sample was collected in question 135. If “unknown,” continue with question 136.

If the bone marrow pathology report states a range for blasts, enter the average of the range rounded to the nearest whole number (e.g., if 0-5%, enter 3%).
If the report indicates “sheets of blasts” or “packed marrow,” report 100%.
If the report states > n% blasts, enter (n+1)% on the form. For example, if the laboratory report indicates > 90% blasts, report 91%.
If the report states < n% blasts, enter (n-1)% on the form. For example, if the laboratory report indicates < 5% blasts, report 4%.

Question 136: Were cytogenetics tested (conventional or FISH)?

Cytogenetic assessment involves testing blood or bone marrow for the presence of a known chromosomal abnormality that reflects the recipient’s disease. Testing methods include conventional chromosome analysis (karyotyping), fluorescence *in situ* hybridization (FISH), and microarray comparative genomic hybridization (aCGH) testing.

Indicate if cytogenetic studies were obtained immediately prior to the start of the preparative regimen.

If cytogenetic studies were obtained, check “yes” and continue with question 137.

If cytogenetic studies were not obtained or it is unknown if chromosome studies were performed, indicate “no” or “unknown” and continue with question 175.

Question 137: Date sample collected

Report the date sample was collected for cytogenetic or FISH testing.

Question 138: Results of tests

If cytogenetic studies identified abnormalities (any karyotype other than 46XX or 46XY), indicate “abnormalities identified” and continued with question 139.

If cytogenetic studies yielded no evaluable metaphases or there were no abnormalities identified, indicate such and continue with question 175.

Questions 139-174: Specify abnormalities.

If question 138 indicates that abnormalities were identified, each of questions 139-173 must be answered as “yes” or “no.” Do not leave any response blank. Indicate “yes” for each cytogenetic abnormality identified at the last evaluation prior to the start of the preparative regimen in questions 139-173; indicate “no” for all options not identified on cytogenetic assessment prior to the start of the preparative regimen. If one or more abnormalities are best classified as “other abnormality,” specify in question 174.

If ≥ 3 cytogenetic abnormalities were identified at the last evaluation prior to the start of the preparative regimen, select “yes” for question 172 (complex, ≥ 3 distinct abnormalities) and specify the corresponding abnormalities in questions 139-171. If any of these abnormalities are not listed among 139-171, report “other abnormality,” and specify in question 174. For example, if the karyotype included -7, +8, and -13, report “yes” for questions 140, 146, 172, and 173/174. Complete the remaining indicators as “no,” and do not leave any response blank.

Question 175: Were tests for molecular markers performed (e.g., PCR)?

Molecular assessment involves testing blood or bone marrow for the presence of known molecular markers associated with the recipient’s disease. Molecular assessments are the most sensitive test for genetic abnormalities and involve amplifying regions of cellular DNA by polymerase chain reaction (PCR), typically utilizing RNA to generate complementary DNA through reverse transcription (RT-PCR).

Indicate if molecular studies were obtained immediately prior to the start of the preparative regimen.

If molecular studies were obtained, check “yes” and continue with question 176.

If molecular studies were not obtained or it is unknown if molecular studies were performed, indicate “no” or “unknown” and continue with question 186.

Question 176: Date sample collected

Report the date the sample was collected for molecular testing.

Questions 177-185: Specify abnormalities

If question 175 indicates that molecular markers were identified, then each of questions 177-184 must be answered as “positive,” “negative,” or “not done.” Do not leave any response blank. If question 184 is answered “positive,” specify the molecular marker identified in question 185.

See Table 2 in this manual for additional information on common molecular markers associated with AML.

Question 186: Was flow cytometry performed?

Flow cytometry assessment is a method of analyzing peripheral blood, bone marrow, or tissue preparations for multiple unique cell characteristics. Its primary clinical purpose in the setting of leukemias is to quantify blasts in the peripheral blood or bone marrow, or to identify unique cell populations through immunophenotyping. Flow cytometry assessment may also be referred to as “MRD,” or minimal residual disease, testing.

Indicate if flow cytometry was performed on a peripheral blood and/or bone marrow sample immediately prior to the start of the preparative regimen.

If flow cytometry was performed, check “yes” and continue with question 187.

If flow cytometry was not performed or it is unknown if flow cytometry was performed, indicate “no” or “unknown” and continue with question 193.

Question 187: Blood

Indicate if flow cytometry was performed on peripheral blood immediately prior to the start of the preparative regimen.

If flow cytometry was performed on a peripheral blood sample, check “yes” and continue with question 188.

If flow cytometry was not performed or it is unknown if flow cytometry was performed, indicate “no” or “unknown” and continue with question 190.

Question 188: Date sample collected

Report the date the peripheral blood sample was collected for flow cytometry analysis.

Question 189: Was disease detected?

Indicate if evidence of disease was detected in the peripheral blood sample sent for flow cytometry analysis. Evidence of disease may include the presence of blasts or an immunophenotype known to characterize the patient’s disease.

If flow cytometry results were consistent with evidence of disease, check “yes.”

If flow cytometry results were not consistent with continued evidence of disease, check “no.”

Question 190: Bone marrow

Indicate if flow cytometry was performed on bone marrow immediately prior to the start of the preparative regimen.

If flow cytometry was performed on a bone marrow sample, check “yes” and continue with question 191.

If flow cytometry was not performed or it is unknown if flow cytometry was performed, indicate “no” or “unknown” and continue with question 193.

Question 191: Date sample collected

Report the date bone marrow sample was collected for flow cytometry analysis.

Question 192: Was disease detected?

Indicate if evidence of disease was detected in the bone marrow sample sent for flow cytometry analysis. Evidence of disease may include the presence of blasts or an immunophenotype known to characterize the patient's disease.

If flow cytometry results were not consistent with continued evidence of disease, check "no."

Q193-201: Disease Status at Last Evaluation Prior to the Start of the Preparative Regimen

Question 193: What was the disease status based on hematologic test results?

Indicate the disease status of AML at the last evaluation prior to the start of the preparative regimen. **See AML Response Criteria for disease status definitions.**

If "1st complete remission," "2nd complete remission," "≥ 3rd complete remission," or "no treatment" is indicated, continue with question 201.

If "primary induction failure," "1st relapse," "2nd relapse," or "≥ 3rd relapse" is indicated, continue with question 194.

Questions 194-200: Specify which of the following [sites] showed active leukemia at last evaluation prior to the start of the preparative regimen

Indicate "yes," "no," or "unknown" for each site specified in questions 194-199. Do not leave any response blank. If "yes" is indicated for "other site," specify the site in question 200. If the patient is not in complete remission, at least one of questions 194-199 must be answered "yes."

Question 201: Date assessed

Enter the date of the most recent assessment of disease status prior to the start of the preparative regimen. The date reported should be that of the most disease-specific assessment within the pre-transplant work-up period (approximately 30 days). Clinical and hematologic assessments include pathological evaluation (e.g., bone marrow biopsy), radiographic examination (e.g., X-ray, CT scan, MRI scan, PET scan), and laboratory assessment (e.g., CBC, peripheral blood smear), in addition to clinician evaluation and physical examination. Enter the date the sample was collected for examination for pathological and laboratory evaluations; enter the date the imaging took place for radiographic assessments.

If the exact date is not known, use the process for reporting partial or unknown dates as described in General Instructions, Guidelines for Completing Forms.