Acute Myeloid Leukemia: Developing Drugs and Biological Products for Treatment

Guidance for Industry

DRAFT GUIDANCE

This guidance document is being distributed for comment purposes only.

Comments and suggestions regarding this draft document should be submitted within 60 days of publication in the *Federal Register* of the notice announcing the availability of the draft guidance. Submit electronic comments to https://www.regulations.gov. Submit written comments to the Dockets Management Staff (HFA-305), Food and Drug Administration, 5630 Fishers Lane, Rm. 1061, Rockville, MD 20852. All comments should be identified with the docket number listed in the notice of availability that publishes in the *Federal Register*.

For questions regarding this draft document, contact (CDER) Donna Przepiorka at 301-796-5358 or Donna.Przepiorka@fda.hhs.gov, or (CBER) Office of Communication, Outreach and Development at 800-835-4709 or 240-402-8010.

U.S. Department of Health and Human Services
Food and Drug Administration
Oncology Center of Excellence (OCE)
Center for Drug Evaluation and Research (CDER)
Center for Biologics Evaluation and Research (CBER)

August 2020
Clinical/Medical

Acute Myeloid Leukemia: Developing Drugs and Biological Products for Treatment

Guidance for Industry

Additional copies are available from:
Office of Communications, Division of Drug Information
Center for Drug Evaluation and Research
Food and Drug Administration
10001 New Hampshire Ave., Hillandale Bldg., 4th Floor
Silver Spring, MD 20993-0002
Phone: 855-543-3784 or 301-796-3400; Fax: 301-431-6353
Email: druginfo@fda.hhs.gov
https://www.fda.gov/drugs/guidance-compliance-regulatory-information/guidances-drugs
and/or
Office of Communication, Outreach and Development
Center for Biologics Evaluation and Research
Food and Drug Administration
10903 New Hampshire Ave., Bldg. 71, Room 3128
Silver Spring, MD 20993-0002
Phone: 800-835-4709 or 240-402-8010
Email: ocod@fda.hhs.gov
https://www.fda.gov/vaccines-blood-biologics/guidance-compliance-regulatory-information-biologics/biologics-guidances

U.S. Department of Health and Human Services
Food and Drug Administration
Oncology Center of Excellence (OCE)
Center for Drug Evaluation and Research (CDER)
Center for Biologics Evaluation and Research (CBER)

August 2020
Clinical/Medical

TABLE OF CONTENTS

Acute Myeloid Leukemia: Developing Drugs and Biological Products for Treatment
Guidance for Industry[1]

This draft guidance, when finalized, will represent the current thinking of the Food and Drug Administration (FDA or Agency) on this topic. It does not establish any rights for any person and is not binding on FDA or the public. You can use an alternative approach if it satisfies the requirements of the applicable statutes and regulations. To discuss an alternative approach, contact the FDA staff responsible for this guidance as listed on the title page.

I. INTRODUCTION

The purpose of this guidance is to assist sponsors in the clinical development of drugs and biological products[2] for the treatment of acute myeloid leukemia (AML). Specifically, this guidance addresses FDA's current thinking regarding the overall development program and clinical trial designs for the development of drugs to support an indication of treatment of AML, including indications limited to an individual phase of treatment (e.g., maintenance, transplantation preparative regimen, etc.).[3]

In general, FDA's guidance documents do not establish legally enforceable responsibilities. Instead, guidances describe the Agency's current thinking on a topic and should be viewed only as recommendations, unless specific regulatory or statutory requirements are cited. The use of the word *should* in Agency guidances means that something is suggested or recommended, but not required.

II. BACKGROUND

AML is a malignant neoplasm arising from a myeloid-lineage progenitor. Although the disease is clonal, the molecular pathogenesis is highly heterogeneous. The International Agency for Research on Cancer classifies AML and related neoplasms on the basis of morphological,

[1] This guidance has been prepared by the Oncology Center of Excellence, the Center for Drug Evaluation and Research, and the Center for Biologics Evaluation and Research in consultation with the Center for Devices and Radiological Health at the Food and Drug Administration.

[2] For the purposes of this guidance, references to drugs include drugs approved under section 505 of the Federal Food, Drug, and Cosmetic Act (the FD&C Act) (21 U.S.C. 355) and biological products licensed under section 351 of the Public Health Service Act (42 U.S.C. 262).

[3] In addition to consulting guidances, sponsors are encouraged to contact the appropriate review division to discuss specific issues that arise during the development of drugs for the treatment of AML.

clinical, and genomic parameters, including specific genetic abnormalities.[4] The median age at diagnosis is 68 years, but the disorder occurs in patients of all ages from neonates to the elderly.[5] For decades, the standard treatment[6] for patients with AML was intensive cytotoxic chemotherapy for induction and consolidation with or without postremission allogeneic hematopoietic stem cell transplantation (HSCT), and the only intent of treatment was cure. Investigations of cytotoxic drugs with or without targeted drugs continue in an effort to increase the fraction of patients with AML who are cured. However, many patients with AML who had just mild pathological or age-related organ impairment at diagnosis were considered to have too high a risk of life-threatening or fatal organ toxicity from such intensive therapy and therefore were offered only palliative treatments or no treatment at all.

New classes of drugs, including drugs that target the specific pathogenetic mutations or a disordered epigenome, are being developed as alternatives to cytotoxic drugs for the treatment of AML. In some cases, these newer approaches may extend survival without the prospect for cure, but extending survival may be a meaningful benefit for patients who would live for only weeks if left untreated. Inducing temporary control of disease with minimal treatment burden and palliation of symptoms are two additional outcomes that might also be considered meaningful in certain circumstances (see discussion in III.B below).

The expansion of treatment intent, broadening of the intended population, and development of a wide range of new drug classes as alternatives to cytotoxic drugs contribute substantially to the complexity of clinical development programs for new drugs for AML. This guidance addresses these considerations and provides recommendations regarding the design and conduct of clinical trials and the types of supporting data that would facilitate efficient development of drugs for the treatment of AML.[7]

III. DEVELOPMENT PROGRAM

A. General Drug Development Considerations

1. Nonclinical

- The Agency's expectations for the nonclinical programs for treatments of malignancies are summarized in the ICH guidances for industry *S9 Nonclinical*

[4] For examples, see Swerdlow SH, Campo E, Harris NL, et al (eds), WHO Classification of Tumours of Haematopoietic and Lymphoid Tissues, 2017. Consult www.iarc.fr for resources with the latest diagnostic criteria for AML classification (accessed July 16, 2020).

[5] National Cancer Institute SEER Stat Fact Sheets: Acute myeloid leukemia. Available from: http://seer.cancer.gov/statfacts/html/amyl.html (accessed July 16, 2020).

[6] See the Glossary for definitions of the AML treatment and disease-related terms used in this guidance.

[7] This guidance does not contain discussion of the general issues of statistical analysis or clinical trial design. Those topics are addressed in the draft ICH guidance for industry *E8(R1) General Considerations for Clinical Studies* (May 2019; when final, this guidance will represent the FDA's current thinking on this topic) and the ICH guidances for industry *E9 Statistical Principles for Clinical Trials* (September 1998) and *E10 Choice of Control Group and Related Issues in Clinical Trials* (May 2001). For the most recent version of a guidance, check the FDA guidance web page at https://www.fda.gov/regulatory-information/search-fda-guidance-documents.

Evaluation for Anticancer Pharmaceuticals (March 2010) and *S9 Nonclinical Evaluation for Anticancer Pharmaceuticals Questions and Answers* (June 2018). These guidances apply to drugs for AML.

- For cellular or gene therapy products being developed for the treatment of AML, sponsors should also consult the guidances for industry *Preclinical Assessment of Investigational Cellular and Gene Therapy Products* (November 2013) and *Long Term Follow-Up after Administration of Human Gene Therapy Products* (January 2020).

2. Devices

- For drugs with a specific therapeutic target, an *in vitro* companion diagnostic device (referred to as a "companion diagnostic" herein) may be essential for the safe and effective use of the drug. Sponsors developing a targeted drug for AML should take into consideration the need for a companion diagnostic early in the drug development timeline.[8]

- Minimal residual disease (MRD) is a biomarker of subclinical tumor burden in patients with AML. In clinical development programs for new AML drugs, MRD assays might be used for selection of patients for participation in protocols, assignment of treatments by prognostic subcategories, or as a measure of efficacy. The guidance for industry *Hematologic Malignancies: Regulatory Considerations for Use of Minimal Residual Disease in Development of Drug and Biological Products for Treatment* (January 2020) provides recommendations about use of MRD and MRD assays in regulatory submissions for drugs or biologics, including those applicable to AML drugs.

3. Clinical Pharmacology

- Patients with AML are commonly prescribed concomitant medication that are substrates, inducers, or inhibitors of cytochrome P450 (CYP) enzymes. In particular, triazole antifungals are moderate to strong CYP3A inhibitors commonly prescribed to reduce the risk of invasive fungal infections in patients with AML. Such drugs may increase the systemic exposure of new AML drugs that are metabolized by CYP3A and may decrease the tolerability of new AML drugs that are CYP3A substrates. Additional studies should be used to address this potential for harm:

  - Sponsors should conduct in vitro metabolism studies to determine if a new AML drug is a substrate, inhibitor, or inducer of CYP3A prior to conduct of the first-in-human (FIH) trial.[9]

[8] For guidance pertaining to companion diagnostics, see the CDRH internet page on companion diagnostics (https://www.fda.gov/MedicalDevices/ProductsandMedicalProcedures/InVitroDiagnostics/ucm407297.htm).

[9] See the draft guidance for industry *In Vitro Metabolism- and Transporter- Mediated Drug-Drug Interaction Studies* (October 2017). When final, this guidance will represent the FDA's current thinking on this topic.

- If an AML drug is a CYP3A substrate, sponsors should proactively incorporate strategies for dose modification with concomitant use of moderate and strong CYP3A inhibitors early in their clinical development programs. If available, sponsors may leverage pharmacokinetic data (e.g., exposure-response relationships for safety and effectiveness, clinical drug interaction studies) from patients with other malignancies who have received the new drug to estimate the potential effect of the co-administration of the new drug with CYP3A inhibitors and determine an appropriate dose of the new drug with moderate or strong CYP3A inhibitors in patients with AML. The development of physiologically based pharmacokinetic models may aid in assessing the effect of some CYP3A modulators on the AML drug and should be considered.

- If the new AML drug is a substrate of, inhibits, or induces any major CYP enzyme or other metabolic enzymes in vitro, sponsors should conduct clinical drug interaction studies to determine appropriate mitigation strategies. FDA's draft recommendations regarding such studies are described in the draft guidance for industry *Clinical Drug Interaction Studies – Study Design, Data Analysis and Clinical Implications*.[10]

- Common supportive care medications for patients with AML, including antimicrobial prophylaxis (e.g., fluoroquinolones) and antiemetics (e.g., 5-HT3 receptor antagonists), are known to prolong the QT interval. Sponsors should conduct an adequate assessment early in clinical development to assess the QT prolongation potential of the AML drug as described in FDA's guidance.[11] If the AML drug has the potential to prolong the QT interval, the protocols should include appropriate strategies for mitigation of QT prolongation, including a list of prohibited concomitant medications associated with QT prolongation and/or more frequent monitoring of ECG and electrolytes, particularly in patients with nausea, vomiting, or diarrhea.

- Patients with AML, especially the elderly, may have impaired hepatic or renal function. Prior to enrolling patients with organ impairment on trials of treatments for AML, the sponsor should identify elimination pathways of the parent drug and its active metabolites. If renal or hepatic elimination pathways are identified, the sponsor should characterize the impact of organ impairment on the pharmacokinetics of the parent drug or active metabolites early in clinical development as described in the FDA's guidances.[12] This provides the basis of dose modifications for patients with organ impairment in late phase clinical studies.

[10] October 2017. When final, this guidance will represent the FDA's current thinking on this topic.

[11] See the ICH guidance for industry *E14 Clinical Evaluation of QT/QTc Interval Prolongation and Proarrhythmic Potential for Non-Antiarrhythmic Drugs* (October 2005).

[12] See the draft guidance for industry *Pharmacokinetics in Patients with Impaired Renal Function — Study Design, Data Analysis, and Impact on Dosing and Labeling* (March 2010) (when final, this guidance will represent FDA's current thinking on this topic) and the guidance for industry *Pharmacokinetics in Patients with Impaired Hepatic Function: Study Design, Data Analysis, and Impact on Dosing and Labeling* (May 2003).

4. Special Populations

a. Pediatric Patients

- FDA encourages sponsors to address the pediatric population early in their clinical development program for drugs for the treatment of AML. For example, adolescent patients should be considered for enrollment along with adults in trials for the treatment of AML.[13]

- When it is not clear that dosing for pediatric patients can be derived with certainty from adult data, or for FIH studies in younger age groups, studies in children should begin with a phase 1 trial of the new drug as monotherapy. The phase 1 monotherapy trial population need not be limited to patients with AML, but the acceptability of the recommended phase 2 dose (RP2D) should be confirmed in a small cohort of pediatric patients with AML before conduct of larger trials for AML in children.

- Section 505B of the Federal Food, Drug, and Cosmetic Act (FD&C Act) requires that certain marketing applications, those for certain drugs that are directed at a molecular target that FDA determines to be substantially relevant to the growth or progression of a pediatric cancer, contain reports of molecularly targeted pediatric cancer investigations, unless a deferral or waiver is granted. The requirement for pediatric investigations applies even if the drug is for an indication for which orphan designation has been granted.[14] Sponsors of molecularly-targeted AML drugs should discuss the applicability of these requirements to their drug as early as end-of-phase 1 to allow sufficient time to develop a pediatric study plan, if needed.[15]

b. Older Adult Patients

- For clinical trials of AML drugs, sponsors should enroll a population that is representative of the age range of patients with the disease. It is acknowledged, however, that older adults with AML may have age-related comorbidities that place them at higher risk for adverse outcomes when treated with intensive chemotherapy. FDA has accepted, but does not require, use of age 75 years as an upper limit for inclusion in trials of intensive chemotherapy. FDA, however, encourages use of no age limit for trials of nonintensive treatments for AML.

- Dose reductions may be required for older patients (e.g., age 65 years and older). Safety, pharmacokinetic, and exposure data from older adults in early phase trials of a

[13] See the guidance for industry *Considerations for the Inclusion of Adolescent Patients in Adult Oncology Clinical Trials* (March 2019) and the guidance for industry and IRBs *Cancer Clinical Trial Eligibility Criteria: Minimum Age Considerations for Inclusion of Pediatric Patients* (July 2020).

[14] For additional information, see the draft guidance for industry *FDARA Implementation Guidance for Pediatric Studies of Molecularly Targeted Oncology Drugs: Amendments to Sec. 505B of the FD&C Act* (December 2019). When final, this guidance will represent the FDA's current thinking on this topic.

[15] For additional information see the guidance for industry *Pediatric Study Plans: Content of and Process for Submitting Initial Pediatric Study Plans and Amended Initial Pediatric Study Plans* (July 2020).

new AML drug should be used to justify the dose or dose modifications of the drug for older adults to be tested in later phase trials.

- FDA recommends an assessment of older adults (e.g., age 65 years and older) for physiologic function at study baseline to assist in identifying subgroups that may be at risk for an adverse outcome when treated for AML. Sponsors may consider using an available geriatric assessment tool or propose a new tool for use in the clinical trials. A simple assessment tool evaluating single or multiple aspects of function with limited burden to the patient is preferred. Sponsors are encouraged to request a meeting as early as possible with FDA to discuss the incorporation of an existing or a new assessment tool for older adult patients in AML clinical trials.

c. Patients with Organ Impairment

- For late phase clinical trials of AML drugs, sponsors should enroll a population that is representative of patients diagnosed with AML, including those with impaired organ function.[16] Appropriate organ impairment studies should have been conducted or the impact of organ impairment on the exposure of the parent drug and its active metabolites assessed adequately to provide appropriate dose modifications as stated in section III.A.3.

- For drugs being developed specifically for the treatment of AML in patients with pre-existing comorbidities that preclude use of intensive chemotherapy, FDA has accepted the following criteria to define the population to be included in the trials that will support marketing approval:

  – ECOG performance status $\geq$ 2,

  – Severe cardiac disorder (e.g., congestive heart failure requiring treatment, ejection fraction $\leq$ 50%, or chronic stable angina),

  – Severe pulmonary disorder (e.g., DLCO $\leq$ 65% or FEV1 $\leq$ 65%),

  – Creatinine clearance < 45 mL/min, and

  – Hepatic disorder with total bilirubin > 1.5 time the upper limit of normal.

FDA will consider additional criteria if sponsors can provide data to justify their proposal.

[16] For additional information, see the guidance for industry *Cancer Clinical Trial Eligibility Criteria: Patients with Organ Dysfunction or Prior or Concurrent Malignancies* (July 2020).

d. Pregnant Patients

- The AML population includes a substantial proportion of young adult females. Pregnant women may be diagnosed with AML during the course of their pregnancy. The standard of care in this circumstance is to administer intensive chemotherapy after the first trimester. As such, pregnant women with AML in certain circumstances may be considered for inclusion in AML clinical trials based on a thorough benefit-risk evaluation and when the trial offers the possibility of direct benefit to the woman and/or fetus that is unavailable outside the research setting.

- Data from relevant nonclinical studies to support safety in pregnant patients should be available prior to enrolling pregnant women in AML clinical trials. In addition, safety data for the drug from previous human exposure, even for indications other than AML, should be included in the assessment of risks.

- When a pregnancy has been identified during an AML clinical trial, the risks and benefits of continuing versus stopping investigational treatment should be reviewed with the pregnant woman. A second informed consent process reflecting additional benefit-risk considerations is advisable for women who choose to continue treatment with the investigational drug during pregnancy.

- Sponsors should consider meeting with FDA early in drug development to discuss when and how to include pregnant women in clinical trials. For a draft of additional general points to consider when pregnant women are included in clinical trials, see the draft guidance for industry *Pregnant Women: Scientific and Ethical Considerations for Inclusion in Clinical Trials.*[17]

5. Safety Reporting Considerations

- Patients with AML may have adverse events due to the underlying leukemia. Additionally, many AML drugs are designed to be myelosuppressive and are expected to result in complications from the cytopenias. Nonclinical studies and the analysis of class effects may also establish expected toxicities for the investigational drug. Sponsors should submit a list of the anticipated serious adverse events that the sponsor does not plan to report individually in an expedited manner to FDA. An IND safety report must be submitted to FDA if an aggregate analysis indicates that the adverse events are occurring more frequently in the drug treatment group per 21 CFR 312.32(c)(1)(i)(C). Additional information can be found in the guidance for industry and investigators *Safety Reporting Requirements for INDs and BA/BE Studies* (December 2012).

- Although investigators are required to report all serious adverse events to the sponsor immediately (312.64(b)), this requirement may be burdensome and not useful when a large proportion of the serious adverse events are expected at a high rate, such as

[17] April 2018. When final, this guidance will represent the FDA's current thinking on this topic.

might occur with the cytopenic complications of treatment of AML. Sponsors may propose an alternative reporting arrangement for investigators in the protocol or in a specific waiver request to FDA, and FDA will provide comment on whether the alternative reporting arrangement is acceptable. For early phase trials, the alternative reporting arrangement is likely to be limited to an alternative timeframe for the investigator to report a serious adverse event to the sponsor; not reporting a serious adverse event at all would be unacceptable.

- Patients with AML may experience relapse while on treatment or during study follow-up. AML-related events, such as relapse or death from relapse, should not be submitted by the sponsor as an IND safety report unless there is evidence suggesting a causal relationship between the investigational drug and the adverse event, such as an aggregate analysis showing that relapse occurred more frequently in the investigational treatment group.

B. Efficacy Endpoints

1. Time-to-Event Endpoints Used Commonly for AML

a. Overall Survival (OS)

- OS is defined as the time from randomization to the date of death from any cause.

- For patients who are alive at the data cut-off, the observations for time-to-event are censored at the last date of documented survival.

b. Event-Free Survival (EFS)

- For studies of drugs for the treatment of AML, EFS is defined as the time from randomization to the date of:

  – Induction treatment failure (ITF),

  – Relapse for those who have induction treatment success (e.g., complete remission (CR)), or

  – Death from any cause,

  whichever comes first. For patients who achieve induction treatment success and are alive and in remission at the data cut-off, EFS should be censored at the last assessment date. See the discussion of duration of remission in section III.B.2.a.

- ITF is defined as failure to achieve the initial interim efficacy endpoint within a prespecified period of time. For example, for studies of intensive induction regimens for first-line treatment of AML, the recommended definition of ITF is failure to achieve morphological CR within 42 days of start of the last cycle of induction

chemotherapy. Because the induction period can be variable and prolonged, it raises ambiguities about how to define time to treatment failure. Therefore, day 1 of treatment should be assigned as the event date for patients with ITF.

- The credibility of the results of EFS analyses are highly dependent on the quality of the data. Many of the data quality issues for EFS are similar to those encountered when using progression-free survival for studies of treatments for solid tumors. For additional general points to consider when using such an endpoint, see the guidance for industry *Clinical Trial Endpoints for the Approval of Cancer Drugs and Biologics* (December 2018).

c. Relapse-Free Survival (RFS)

- RFS may be acceptable as an endpoint specifically in studies of treatments for patients with AML in remission, such as the consolidation or maintenance phases.

- For studies of drugs for the treatment of AML, RFS is defined as the time from randomization to the date of relapse or the date of death from any cause, whichever comes first. For patients alive and in remission at the data cut-off, RFS should be censored at the last assessment date.

d. Statistical Considerations for Time-to-Event Endpoints

- The general principles for the design and analysis of clinical trials as outlined in ICH *E9* apply to trials of treatments for AML. The bullets below are additional considerations specific to AML trials and can also be thought of as discussing specific attributes of the estimand concept, which is further discussed in the draft ICH guidance for industry *E9(R1) Statistical Principles for Clinical Trials: Addendum: Estimands and Sensitivity Analysis in Clinical Trials*.[18]

- For time-to-event endpoints in a randomized trial for AML, the primary analysis set consists of all randomized subjects. With respect to the primary analysis method, FDA has accepted the log-rank test. Although FDA is open to discussion about other methods, it is incumbent on the sponsor to provide the required justification. Additional summary metrics that should be reported include the estimated medians (where meaningful), hazard ratios, and 95% confidence intervals.

- It is common for some but not all patients with AML to undergo allogeneic HSCT after or in conjunction with an investigational drug, which may impact EFS or RFS. Additionally, as more effective drugs for AML are approved, post-study treatment may impact OS. As these treatments are integral to the practice of medicine, the primary analysis of these endpoints should be conducted without censoring for such

[18] June 2017. When final, this guidance will represent the FDA's current thinking on this topic.

treatment.[19] For additional discussion about survival analyses when HSCT is a post-study treatment, see Appendix 2.

- Trials designed to cure AML often result in survival contours characterized by an initial drop followed by a plateau. For additional discussion about analysis when there is a survival plateau, see Appendix 2.

- Secondary and sensitivity analyses of time-to-event endpoints should follow a prespecified statistical analysis plan. These analyses may include the use of alternatively-defined endpoints (e.g., alternative definition of time to ITF other than day 1 when using EFS), alternatively-defined populations, or using alternative analysis methods.

2. Binary Endpoints Used Commonly for AML

a. Complete Remission (CR)

- For documentation of CR, FDA has used the following definition:

  – Marrow blasts < 5% by morphological examination,
  – Absolute neutrophil count (ANC) > 1 Gi/L,
  – Platelet count > 100 Gi/L,
  – Absence of leukemic blasts in the peripheral blood by morphological examination, and
  – No evidence of extramedullary disease.

- The protocol should provide for maximum windows of time between marrow sampling and peripheral blood tests used to establish CR. For the response assessment of extramedullary disease, invasive testing should be limited only to sites involved with AML at baseline that cannot be evaluated directly by general physical examination, unless invasive testing is considered standard of care. The date of marrow sampling is assigned as the CR date. Missing data is considered failure to achieve CR. Additional considerations may be needed depending on the extent of missingness, how differential it is between the arms when the AML study is randomized, and whether the study is open-label. See section III.D.4 for a discussion of trial procedures critical to the assessment of CR and section IV.B.1 for the discussion of the adjudication of CR for the purpose of labeling.

- For CR, the duration of remission (DOR) is defined as the time from CR to hematological relapse or death from any cause, whichever comes first. Adequate follow-up is required in order to establish that the durability of CR is meaningful.

[19] See the draft treatment policy discussion in the draft ICH *E9(R1)*. When final, this guidance will represent the FDA's current thinking on this topic.

- Hematological relapse is defined as marrow blasts > 5% by morphology, persistent reappearance of blasts in the peripheral blood by morphology, or the occurrence of extramedullary disease. In general, once CR is confirmed by marrow examination, further follow-up for relapse may be limited initially to physical examination and peripheral blood tests. The known time to relapse for the regimen in the control arm or from other historical data should be used when planning the frequency and duration of testing for relapse, but in order to determine DOR, EFS, and RFS as accurately as possible, the assessments would likely be performed more frequently than in standard practice. When relapse is suspected on the basis of the follow-up physical examination or peripheral blood counts, additional testing may be performed to confirm the finding, but the date of relapse is set to the date of the first test that suggests relapse.

b. CR with Partial Hematological Recovery (CRh)

- Use of CRh as an endpoint is applicable to drugs that are relatively nontoxic and nonmyelosuppressive, as might be used for palliative purposes.

- For documentation of CRh, FDA has used the following definition:

  – Marrow blasts < 5% by morphological examination,

  – ANC > 0.5 Gi/L and platelet count > 50 Gi/L, but the count recovery criteria for CR are not met,

  – Absence of leukemic blasts in the peripheral blood by morphological examination, and

  – No evidence of extramedullary disease.

- Since the potential utility of CR as an endpoint is similar to that of CRh in this setting, the actual endpoint used is CR+CRh. Adequate follow-up is needed in order to establish that the durability of CR+CRh is meaningful.

c. Transfusion-Independence (TI)

- Durable TI as an endpoint is applicable to drugs that are relatively nontoxic and nonmyelosuppressive, as might be used for palliative purposes.

- When durable TI is used, this endpoint should be supported by evidence showing an effect of the treatment on an endpoint reflecting antileukemia activity. TI as an endpoint for the treatment of AML should also be distinguished from TI as used in the evaluation of hematopoietic growth factors (e.g., for the treatment of anemia) where the effect of the drug is directed at normal hematopoietic cells rather than at the leukemia.

- TI is defined as the absence of red blood cell and platelet transfusions for a prespecified period of time during continued treatment. The credibility of the data is dependent on the protocol specifying the minimal parameters for use of transfusions and documentation that the instructions were followed. Hence, an important supporting analysis would include an assessment of serial measurements of hemoglobin and platelet counts to ensure that the observed TI was an actual treatment effect and not a bias in the administration of transfusions by the investigator.

- TI should be assessed as a response achieved in the subgroup of patients who were transfusion dependent (TD) at baseline (conversion from TD to TI with treatment) separately from the subgroup of patients who were TI at baseline (maintenance of TI with treatment). For patients with active AML, transfusion dependence at baseline is based on the receipt of any red blood cell or platelet transfusions within at least 28 days prior to the start of study treatment. Analyses of red blood cell TI and platelet TI separately should be used to establish consistency of the components of the TI endpoint.

d. Statistical Considerations for Binary Endpoints

- For single-arm AML trials, the analysis set consists of all patients treated with investigational drug.[20] If the labeling claim is limited by the target of the drug (e.g., AML with a FLT3 mutation for a drug that is a FLT3 inhibitor), the analysis set should include only those patients confirmed positive for the target using the proposed companion diagnostic or bridged clinical trial assay. For binary endpoints, proportions and their 95% confidence interval should be reported.

- For randomized AML trials, the analysis set consists of all randomized patients. For binary endpoints, the primary analysis may be based on Fisher's Exact test; the Cochran-Mantel-Haenszel test may apply when stratification factors were used at randomization. Proportions and their 95% confidence intervals should be reported. Any additional metrics to quantify the treatment effect, such as the difference in proportions, ratio of proportions or odds ratio, should be prespecified. For targeted drugs, a secondary analysis should be performed where the analysis set is restricted to patients confirmed positive for the target.

- DOR may be calculated using the Kaplan-Meier method using relapse or any-cause death as events. Estimated median and range should be reported. When the number of study subjects is small, or when follow-up is short, the Kaplan-Meier estimate may not be stable. In this circumstance, the observed median and range of observed DOR may be reported. Sensitivity analyses may include calculation of DOR including nonprotocol antileukemia treatment in the absence of documented relapse as an additional event, or calculation of DOR with censoring at HSCT.

[20] In cases of personalized products with the potential for a high rate of manufacturing failure, additional efficacy analyses based on enrolled patients may be needed even in a single-arm trial in order to assess the impact of manufacturing failure on the efficacy endpoint.

493 *3. Minimal Residual Disease (MRD)-Based Endpoints*
494
495 • For new drugs that have a demonstrated durable CR in patients with relapsed or
496 refractory acute leukemia, FDA has accepted marrow MRD of less than 0.01% as
497 supporting evidence of efficacy. As technologies improve and new clinical findings
498 emerge, the level of MRD needed to support an efficacy claim for AML may change.
499
500 • CR as defined in section III.B.2 is the preferred timing to assess MRD as a response
501 endpoint. If assessments are made at CR without count recovery (CRi), or at lesser
502 responses, to support a claim of efficacy, the sponsor should include data to justify
503 the validity of the plan. The recommended analyses of MRD-based response
504 endpoints are similar to those for CR discussed in section III.B.2. When used as a
505 binary endpoint, the denominator for the analysis of MRD response should be all
506 treated patients (single-arm trial) or the ITT population (randomized trial), and the
507 numerator should be all patients who achieved CR and the required level of MRD.
508 Missing data should be imputed as a failure.
509
510 • Using MRD-based definitions to identify relapse for the purposes of determining
511 DOR, EFS, or RFS can be challenging in studies of new treatments for AML, since
512 that would require frequent marrow sampling. It may be more practical to monitor
513 for hematological relapse as described in section III.B.2 for the DOR, EFS, and RFS
514 definitions unless there is a validated MRD assay using peripheral blood samples.
515
516 • For additional information on the use of MRD as an efficacy endpoint, see the
517 guidance for industry *Hematologic Malignancies: Regulatory Considerations for*
518 *Use of Minimal Residual Disease in Development of Drug and Biological Products*
519 *for Treatment*.
520
521 *4. Other Potential Measures of Efficacy for AML*
522
523 • FDA acknowledges that as technology progresses and clinical trial data accumulate,
524 alternative biomarkers or measures of efficacy may be proposed for use as endpoints
525 in AML clinical trials. When considering the use of efficacy endpoints other than
526 those listed above, especially in a trial to be used to support a marketing application,
527 sponsors should obtain advice from FDA about the acceptability of the proposed
528 novel endpoint prior to initiating the trial.
529
530 • Key efficacy endpoints may also include well-defined and reliable patient-focused
531 outcome measures. When used as the basis of a claim of treatment of AML, such
532 endpoints should be supported by data showing that the treatment also has a direct
533 effect on the leukemia. For additional information, refer to the guidance for industry
534 *Patient-Reported Outcome Measures: Use in Medical Product Development to*
535 *Support Claims* (December 2009).
536

- Sponsors planning to use real world data[21] to support an AML drug marketing application should obtain advice from FDA at the time of protocol development to ensure that the data sources will provide the data needed to assess the treatment effect. Important considerations include whether the sources capture the data elements (e.g., marrow results, peripheral blood differentials, etc.) to derive clinically accepted endpoints for demonstrating efficacy, and if so, the extent of misclassification, the timing of assessment, and the frequency of assessment. Sponsors should plan for additional discussions regarding alternative measures if the data sources do not capture the key elements of the clinically accepted endpoints.

C. Exploratory Trial Considerations

1. First-in-Human (FIH) Trials

- Conducting an FIH trial in patients with rapidly progressing acute leukemias has several challenges; the doses used in the first cohorts may be subtherapeutic, and the assessment of toxicity may be confounded by adverse events due to the underlying leukemia. Where feasible, sponsors should consider alternative designs for the FIH trial that would identify a pharmacologically-active dose before commencing the dose-escalation trial in patients with AML. For example, the sponsor may consider a limited window study over a short interval (days to weeks) prior to the administration of a standard treatment or conducting the initial dose escalation in patients with more slowly growing tumors (solid tumors or lymphoma). Where applicable, sponsors may also consider the FDA's Model Informed Drug Development (MIDD)[22] pathway to help select the appropriate doses for efficacy and safety evaluation.

- Historically, the most effective regimens for the treatment of AML have been combination regimens. Nonetheless, the FIH trial should be limited to assessment of one drug at a time, and study of the combination should not commence until there is adequate information about safety and tolerability of the individual drugs. Rare exceptions to this principle are described in the guidance for industry *Codevelopment of Two or More New Investigational Drugs for Use in Combination* (June 2013).

- An FIH trial of a myeloablative drug to be used as a single-agent preparative regimen for HSCT for the treatment of patients with AML may be feasible, but prior to submission of the investigational new drug application (IND), sponsors should obtain advice from FDA about the optimal approach for development of such drugs. An FIH trial of a new drug in combination with a preparative regimen is rarely acceptable.[23]

[21] For additional information, see "*Framework for FDA's Real-World Evidence Program*" at https://www.fda.gov/media/120060/download and the draft guidance for industry *Submitting Documents Using Real-World Data and Real-World Evidence to FDA for Drugs and Biologics* (May 2019). When final, this guidance will represent the FDA's current thinking on this topic.

[22] See the *Federal Register* (83 FR 16868, April 17, 2018).

[23] An example of an exception would be for a cell therapy where there is no scientific justification for study of the cell therapy in the absence of a prespecified standard preparative regimen.

- Although many drugs developed for the treatment of AML are highly myelosuppressive and/or genotoxic, in select cases it may be possible to conduct the FIH trial in healthy volunteers. The advantage to this approach is that the safety profile may be simpler to determine in the absence of confounding adverse events due to the underlying leukemia. FDA recommends that sponsors request feedback on the design of FIH trials of new AML drugs in healthy volunteers, including the limitations in exposure and other restrictions needed to protect healthy volunteers participating in such studies.[24]

- For AML drugs that are CYP3A substrates, sponsors should consider enrolling patients on azole antifungals or other CYP3A inhibitors in FIH trials to generate data needed to select a safe dose with these concomitant drugs (see section III.A.3).

- Sponsors developing cellular or gene therapy products for the treatment of AML should also consult the guidance for industry *Considerations for the Design of Early-Phase Clinical Trials of Cellular and Gene Therapy Products* (June 2015) and the guidance for industry *Long Term Follow-Up after Administration of Human Gene Therapy Products.*

2. Exploratory Trial Population

- For dose-escalation trials being conducted to determine the maximum tolerated dose (MTD), the eligible population is usually limited to patients who have failed all conventional drugs. Patients with subtypes of AML that respond very poorly to conventional drugs, such as those with high-risk genetic abnormalities, might also be considered for such trials even without prior treatment, but if doing so, the consent form should clearly state the implications of foregoing conventional drugs in order to participate in the clinical trial.

- The benefit-risk ratio for participation in a dose-escalation trial may also be acceptable for patients with MRD after treatment with conventional drugs for AML, but such protocols should include a description of the evidence that justifies the risks of such a study compared to the prognosis based on the level of MRD proposed for eligibility.

- For dose-escalation trials being conducted to determine the RP2D, the eligibility criteria that address organ function and comorbidities should be commensurate with the target patient population. For example, if developing a drug for the treatment of AML in patients with renal or hepatic impairment, including patients with only normal renal or hepatic function might conclude with a dose that is safe in patients with normal organ function but that is too toxic for the target population with organ impairment.

[24] See also the guidance for industry *Estimating the Maximum Safe Starting Dose in Initial Clinical Trials for Therapeutics in Adult Healthy Volunteers* (July 2005).

- Multiple genetic mutations and molecular pathways have been identified as contributing to the pathogenesis and persistence of AML. For new drugs proposed to target these mutations or pathways, the clinical development program should have an early phase trial that includes patients with and without the putative target in order to assess the need in later phase trials to select patients based on the presence of the target. Including marker-negative patients might not be necessary for drugs that target a cell surface receptor, especially when preclinical data suggest no potential for a therapeutic effect in the absence of the cell surface receptor.

3. Dose-Escalation Trials

- For dose-escalation trials, the general principles for selection of the safe starting dose and the frequency of administration as described elsewhere[25] also apply to drugs being developed for the treatment of AML. As discussed in section III.C.1, the safe starting dose for a study in patients with active AML may differ from the starting dose for a study in healthy volunteers. The nonclinical data should also be used to determine the slope of the dose-toxicity curve, the anticipated therapeutic dose range, and the maximal exposure in order to plan the increments in dose between cohorts in the escalation. For drugs that are CYP3A substrates, the selection of a safe starting dose should also consider the concomitant use of drugs that are CYP3A4 inhibitors such as azole antifungals (see section III.A.3).

- The protocol should describe the specific rule-based or model-based criteria used to guide the decision on whether to proceed with escalating the dose in subsequent cohorts. For dose-escalation trials of conventional outpatient chemotherapy for patients with cancer, escalation to higher doses is generally limited by the rate of severe, life-threatening, or fatal events (grades 3-5) termed dose-limiting toxicities (DLTs), and the MTD as identified by the 3+3 rule has no more that 17% DLTs. This paradigm, however, is not applicable to all types of treatments for AML. For example, such a rule would allow far greater toxicity than acceptable for continued treatment or maintenance that extends for years. On the other hand, the rule would likely result in premature closure of a trial of a preparative regimen for HSCT, where grade 3 toxicities are common. Hence, the criteria proposed to guide dose-escalation decisions should take into account the types, severities, and rates of toxicities accepted with standard regimens of similar intensity in the intended population (see Appendix 1 for examples). The protocol should describe the data that support the assumptions used to develop the criteria for guiding dose-escalation.

- For many cytotoxic drugs used for the treatment of AML, there is a strong dose-response effect, and in order to achieve the highest response rate, the cited goal of the dose-escalation trial is to identify the MTD. This is not necessarily true for targeted drugs, for which the pharmacodynamic effect may plateau at doses lower than maximally-tolerated. Hence, the goal of the dose-escalation trial should be to

[25] See ICH *S9* and ICH *S9 Questions and Answers*.

determine the RP2D instead. The protocol should include a definition of the RP2D, and the determination of the RP2D should take into consideration the safety, tolerability, pharmacokinetic, pharmacodynamic, and efficacy data (see also section III.D.2).

- Based on the design of the dose-escalation trial, participants in the initial cohorts of the trial may not receive optimal treatment, which may be a disadvantage for patients with active AML who are in need of cytoreductive treatment. Despite the desire to ensure that patients with AML are treated with pharmacologically-active doses of drug, intra-patient dose-escalation based on lack of very early response may not be scientifically valid; a complete characterization of safety, tolerability, and efficacy at any dose level usually requires treatment for multiple cycles. Intra-patient dose-escalation may be considered in select circumstances where risks can be minimized objectively. For example, if there is an established pharmacodynamic biomarker for safety, intra-patient dose escalation may be feasible with frequent monitoring of the biomarker. Additionally, for patients who have received multiple cycles of treatment without evidence of cumulative toxicity or therapeutic activity, it may be beneficial to escalate the individual patient's dose to a higher level if that higher dose has been established as safe in subsequent cohorts. The protocol should specify the criteria for when intra-patient dose escalation is allowed, how the new dose is assigned, any changes in the monitoring plan needed to accommodate the change in dose, and how the safety and efficacy data will be evaluated for such patients.

- The planned duration of treatment should be described clearly in the protocol. Long-term treatment may be considered in the dose-escalation trial, typically for patients with relapsed or refractory AML, but there should be objective criteria for when to discontinue treatment permanently, including high-grade toxicities. When treatment in the dose-escalation trial is planned to extend beyond achievement of CR, a rationale should be provided for the proposed duration of treatment after remission. For patients who are taken off the investigational drug after achieving a CR, the protocol may also address retreatment in case of relapse.

- Early phase trials are also the place to determine the expected time to response, allowing study treatment to continue in the absence of toxicity unless prespecified levels of disease response have not occurred within a maximum number of cycles. Such information will provide support for the treatment plan proposed for confirmatory trials designed to test for efficacy.

- For early phase trials of intensive AML drugs given with curative intent, a maintenance phase is generally not acceptable in settings where there is no established benefit of maintenance; in such cases, a randomized control arm is recommended.

- Certain toxicities of treatment, such as anemia or tumor lysis syndrome, are expected with almost any treatment of patients with AML. Treatment of such usual toxicities is considered standard practice, and detailed instructions on the practice of medicine

need not be included in the protocol unless a specific treatment is critical for safe use of the investigational drug. Based on established class toxicities, mechanism of action and/or nonclinical studies, there may also be unusual drug-specific toxicities, such as differentiation syndrome or cytokine release syndrome. Until treatment is standardized in practice, instructions for management of patients with such unusual drug toxicities should be included in the protocol.

4. Exploratory Expansion Cohorts

- A small cohort of 6-12 subjects treated at the presumptive RP2D can be useful to confirm safety prior to start of additional trials. In the absence of data from a safety expansion cohort, the confirmatory trial should include a very early interim safety analysis to corroborate safety of the RP2D.

- When the new drug is being studied as an add-on and the background regimen has substantial toxicity (i.e., a standard intensive AML induction regimen), a randomized comparison may be necessary to detect even large differences in toxicity that might not be noticed in the single-arm setting.

- Responses as defined in section III.B.2 are generally acceptable measures of activity that should be included in exploratory early phase clinical trials in AML. Lesser responses (e.g., partial remission, shorter term transfusion-independence, etc.) may reflect activity of the drug, but such lesser responses should guide development to alternative strategies to leverage that activity (i.e., different schedules or use in combinations) rather than being viewed as a success.

- A small cohort of patients treated at the presumptive RP2D can also be used to provide an estimate of efficacy to support design of additional trials. Such a cohort generally includes approximately 20 subjects. Large single-arm expansion cohorts solely for exploratory purposes are discouraged. Any large single-arm trial should have a design based on clear hypothesis testing, and the protocol should include justification of the sample size proposed.

- Time-to-event endpoints are difficult to interpret in single-arm trials and, therefore, are generally not useful in assessing efficacy in exploratory early phase trials. Data for such endpoints, however, should still be collected, since such data could be useful in designing the confirmatory trials if other objective measures of efficacy support further development of the drug.

- To ensure the safety of study participants, the expansion cohort plan should include stopping rules for excessive toxicity that would require pausing enrollment to evaluate whether the treatment plan should be modified. The acceptable rate and type of toxicities will depend on the treatment setting as discussed for development of DLT criteria in section III.C.3. The protocol should describe the exact bounds for the stopping criteria, the statistical method used to calculate the bounds, and the basis for the clinical assumptions used in the calculation. FDA recommends that the bounds be

calculated using nonstringent parameters (i.e., 70% power or 80% posterior probability), so that the trial can be paused at the earliest sign of excessive toxicity. For patients with active AML, toxic events for stopping rules might include treatment-related deaths, prolonged neutropenia lasting past cycle day 42 in the absence of disease, and high-grade nonhematological adverse reactions.

D. Confirmatory Trial Considerations

1. Confirmatory Trial Population

- The protocol should use the most updated diagnostic criteria for AML or for a specific AML type to describe the eligible population. Sponsors should seek advice from FDA rather than using outdated criteria solely to match a population used in support of a past approval.

- Patients with newly-diagnosed AML, patients with AML in late first relapse (e.g., first remission > 6 months), and patients with other relapsed or refractory AML (e.g., primary refractory, early first relapse, and any second or later relapse) represent three distinct indications. A separate trial for each indication is recommended, but separate cohorts in a single trial may be used for analyses to support each indication independently. In the latter circumstance, the protocol should describe clearly the eligibility criteria for each cohort. HSCT is considered standard practice in the treatment of AML, and relapse post HSCT would fall under either treatment of first relapse or treatment of later relapse rather than being a separate indication.

- For clinical trials of a biomarker-selected AML population, the eligibility criteria should state clearly what assay is to be used to select patients with the cognate target, the tissue (blood, marrow, etc.) used for the assay, and the level of the target needed to meet eligibility.

- For clinical trials planned to support a marketing application for the intended population of patients with comorbidities that preclude use of intensive induction chemotherapy, the eligibility criteria should include detailed parameters that describe the population. See section III.A.4.c for examples of criteria for organ impairment that FDA has accepted to describe this subgroup of patients for AML trials.

- For clinical trials being designed to support a marketing application, the eligibility criteria should reflect the characteristics of the general population with AML. Exclusion criteria should be limited to disease- or patient-related factors associated with a lack of benefit or an unacceptable risk of toxicity from the investigational drug based on data in early phase trials.[26]

[26] For additional discussion, see the draft guidance for industry *Enhancing the Diversity of Clinical Trial Populations — Eligibility Criteria, Enrollment Practices, and Trial Designs* (June 2019). When final, this guidance will represent the FDA's current thinking on this topic.

- For clinical trials of noncurative drugs for AML, the eligibility criteria should specifically exclude patients willing and able to receive intensive curative treatment.

2. Dose Selection and Treatment Plan

- The dose and schedule of the investigational drug in the treatment regimen should be optimized before initiating the confirmatory trials. Clinical pharmacokinetic data, pharmacodynamic data, clinical activity measures, clinical safety data, and nonclinical pharmacology data, should be pooled for conduct of integrated dose-response and exposure-response analyses for activity and safety for dose optimization. The results of such analysis should be included in the protocol to justify the dose.

- For drugs planned to be administered for multiple cycles, and especially for drugs given long-term on an outpatient basis, tolerability should be taken into consideration when choosing the dose to be used in the confirmatory trial. In general, for drugs planned to be given long-term or over multiple cycles, it is expected that dose modifications or discontinuations for adverse reactions are limited to less than 20% of the patients, and that at least 80% dose intensity is achieved over multiple cycles for at least 80% of the patients.

- The protocol should include dose adjustment strategies for specific populations (e.g., with organ impairment or with concomitant use of moderate and strong CYP3A modulators) and in response to emerging adverse events. The experience with these instructions during study conduct provides the basis for dose modification instructions in labeling.

3. Confirmatory Trial Design

a. General Considerations for Confirmatory Trial Designs

- The principles of designing trials to demonstrate efficacy for the purposes of supporting a marketing application are described in general guidance,[27] and these general principles are applicable to trials for AML drugs. The bullets below provide additional advice specific for the trials of treatments for AML.

- To prevent bias in study conduct or in selection of poststudy treatments, the use of blinded treatments where feasible is recommended for randomized trials.

- The use of specific genetic targets and other prognostic factors used for eligibility or risk stratification should be described in detail. For patients with relapsed or

[27] See the draft ICH *E8(R1)* and *E9(R1)* (when final these guidances will represent the FDA's current thinking on these topics); the ICH guidances for industry *E9* and *E10*; and the draft guidance for industry *Demonstrating Substantial Evidence of Effectiveness for Human Drug and Biological Products* (December 2019) (when final, this guidance will represent the FDA's current thinking on this topic).

refractory AML, the protocol should state clearly whether these prognostic factors are measured at the time of diagnosis or at the time of relapse.

- Because treatment for AML involves discrete stages of treatment with different goals, the purpose of treatment with the investigational drug should be stated clearly in the protocol. Potential objectives may include remission induction alone, remission induction followed by consolidation, consolidation of remission alone, remission maintenance (after chemotherapy or transplantation), or control of complications of the disease in the relapsed/refractory setting.

- If the clinical trial has goals in multiple stages of treatment, sequential randomizations may be needed. For example, if a maintenance indication is planned in addition to initial treatment, patients should be rerandomized prior to maintenance to allow for isolation of the treatment effect of study drug(s) during maintenance.

- A detailed statistical analysis plan stating the trial hypotheses, sample size, analysis timing, and analysis methods should be submitted before trial initiation. The sample size calculation should be based on the expected efficacy in the control arm and the anticipated treatment effect of the investigational drug with respect to the primary endpoint in the planned patient population. Estimating the outcome for the control arm in a molecular subgroup may be challenging for treatments of AML with new molecular targets that were not studied previously with standard care regimens. When there is little extant data to support the assumptions for the anticipated treatment effect, sponsors may consider an adaptive design or other novel approach.[28] In such a case, the sponsor should request feedback from FDA on the proposed design prior to initiating the trial.

- When the design requires an active comparator, the treatment should be standard of care for the study population (e.g., study drug vs. 7+3). Placebo comparators may be considered in add-on trials (e.g., study drug+7+3 vs. placebo+7+3) if appropriate treatment for the control arm. Comparative efficacy studies of combinations that do not isolate the effect of the study drug (study drug+azacitidine vs. 7+3) may also be acceptable if the control is standard of care for the population, the activity of the study drug was demonstrated in other trials, and the contribution of each drug in the new regimen is supported by other data in the context of use.

- It is common for multiple efficacy endpoints (i.e., OS, EFS, CR) to be assessed in a clinical trial for AML. The statistical analysis plan should prespecify a multiple testing strategy for important secondary endpoints that adjusts for multiplicity conditioned on demonstrating a positive outcome for the primary endpoint. Note that effects on secondary endpoints are generally not sufficient to support a marketing application in the absence of demonstration of an effect on the prespecified primary endpoint. Additionally, even if an effect on a secondary endpoint is demonstrated, it may not be acceptable for labeling if it is not an established efficacy endpoint; for

[28] For example, see the guidance for industry *Adaptive Designs for Clinical Trials of Drugs and Biologics* (November 2019).

example, the composite of CR+CRi may not be suitable for labeling due to the inclusion of CRi.

- In large randomized trials, an interim analysis for futility is strongly recommended to ensure that the benefit-risk ratio for enrolled patients continues to be favorable. FDA has accepted group sequential/early stopping designs for interim analyses. However, for certain endpoints, such as EFS or RFS, FDA discourages early stopping for efficacy based on a positive assessment at the interim analysis. More follow-up may be needed to assess other important endpoints, such as duration of response and safety, that would be needed to determine the overall benefit-risk. FDA is willing to discuss the potential pitfalls in a timely fashion when the sponsor is considering early study termination based on interim efficacy analysis results.

- The timing of analysis of continued response (e.g., DOR, RFS, etc.) should be prespecified to mitigate bias in study result interpretation.

b. Treatment of AML with Curative Intent

- Treatments with an expectation of a survival plateau are considered treatment with curative intent. Examples include standard intensive chemotherapy as first-line treatment for AML.

- FDA has accepted OS, EFS, and RFS as clinical endpoints that represent clinical benefit for traditional approval for treatments with curative intent.

- AML is a heterogenous disease, and historical controls are severely limited in their ability to accurately parallel the intended population for the indication. Therefore, the use of historical controls in AML is not appropriate for studies of treatment with curative intent. Trials intended to support a marketing application for this indication should have a randomized control arm.

c. Treatment of AML without Curative Intent

- Treatments with no expectation of a survival plateau, but where the goal is to extend survival or greatly improve durable CR relative to a control, are considered treatment without curative intent for AML.

- FDA has accepted OS and EFS as clinical endpoints that represent clinical benefit for traditional approval for treatments without curative intent. For studies in populations with a very high rate of induction treatment failure or when OS is expected to be short, OS may be the more practical endpoint to establish clinical benefit. Durable CR may also support traditional approval depending on the disease setting and benefit-risk ratio.

- Trials intended to support a marketing application for this indication may be randomized or single-arm in design, depending on the endpoint, patient population,

and available therapy. FDA recommends that sponsors request advice from FDA on proposed study designs for this indication.

d. Treatment of AML with Palliative Intent

- Nonintensive treatments without substantial associated toxicities administered with the goal of temporary disease control and minimal treatment burden are considered treatment with palliative intent in AML.

- Durable TI may represent a direct clinical benefit resulting from the relief from the burdens of insufficient hematopoiesis due to active AML. FDA has accepted durable CR and durable CR/CRh with TI as clinical endpoints that represent clinical benefit for traditional approval for treatments with palliative intent.

- Trials intended to support a marketing application for this indication may be randomized or single-arm in design depending on the endpoint, patient population, and available therapy. Best supportive care may be acceptable as a comparator in a randomized trial only for a patient population without available therapies. In certain clinical settings, a single-arm trial may be appropriate for traditional approval if there are adequate historical data to support the null hypothesis.

4. Confirmatory Trial Procedures

- Baseline demographic and disease characteristics are used to ensure consistency of the benefit-risk by subgroup analyses. The following key AML-specific information should be documented and collected on the case report forms:

  – Disease (WHO-based diagnosis[29]),

  – Disease status at enrollment (e.g., newly-diagnosed, 2nd relapse, etc.),

  – Response status at enrollment (primary refractory vs. untreated vs. refractory relapse),

  – Duration of first remission,

  – Genetic profile and/or risk group at diagnosis and at enrollment (use of the most contemporary accepted risk stratification is recommended),

  – All prior treatments for AML,

  – Baseline functional assessments (where applicable, geriatric assessment is recommended), and

[29] See footnote 4.

- Relevant comorbidities (see section III.A.4.c).

- Patients with AML receiving intensive chemotherapy or high-dose chemotherapy for transplantation are expected to have a high rate of low-grade adverse reactions. For studies of drugs with well-established safety profiles, consideration should be given to collection of a limited amount of safety data.[30] For new drugs with unclear safety profiles, all adverse events should be collected regardless of grade or attribution.

- To ensure that data will be available for the assessment of potential interactions between new drugs and other drugs used commonly for patients with AML, the dates and doses of concomitant medications, especially antifungal medications, should be accurate.

- To assess confounding in efficacy analyses due to subsequent post-study treatments, the following post-study information should be documented and collected on the case report forms:

  - At least the first post-study salvage treatment and the reasons for the treatment choice and

  - HSCT and CAR T cell dates for patients proceeding to transplantation with an on-study response or as a post-study salvage treatment.

IV. REGULATORY SUBMISSIONS

A. Investigational New Drug Applications

- General requirements for INDs apply to AML. See sections III.A and III.C for recommendations on submission of FIH trials in AML as the IND-initiating study. Sponsors may request advice from FDA through the pre-IND program.

- FDA supports the use of innovative trial designs, such as master protocols, for efficient drug development in AML. For IND submissions that contain innovative trial designs, FDA recommends consultation through the pre-IND program. For additional draft recommendations, see the draft guidance for industry *Master Protocols: Efficient Clinical Trial Design Strategies to Expedite Development of Oncology Drugs and Biologics.*[31]

- A companion diagnostic may be essential for patient selection in IND protocols for targeted AML drugs. Sponsors may request a study risk determination directly from CDRH or in concert with the IND (see the guidance for industry *Investigational In*

[30] See the guidance for industry *Determining the Extent of Safety Data Collection Needed in Late-Stage Premarket and Postapproval Clinical Investigations* (February 2016).

[31] September 2018. When final, this guidance will represent the FDA's current thinking on this topic.

Vitro Diagnostics in Oncology Trials: Streamlined Submission Process for Study Risk Determination (October 2019) to determine whether an IDE is needed). See also section III.A.2.

B. Marketing Applications

1. Assessment of Efficacy

- Assessments of efficacy in AML clinical trials are generally based on objective criteria, such as neutrophil counts and marrow blast percentage. To allow FDA to confirm the analyses of the treatment effect, the raw data supporting the study endpoints should be submitted in the marketing application.

  – If bone marrow pathology results exceed the character limit for a variable in an xpt file, a pdf of the report may be acceptable.

  – To assist with the adjudication of responses, the submission should include a summary response file (see Appendix 3) for the confirmatory study and for the integrated efficacy population.

  – For studies with an endpoint of TI (see section III.B.2.c), the submission should include a summary transfusion analysis data file (see Appendix 3) for at least the confirmatory study.

  – To assist with the assessment of response and TI, the submission should include a file with the dates of RBC and platelet transfusions and the number of units transfused.

2. Assessment of Safety

- Patients with AML have a high background of adverse events due to the leukemia. Assessment of toxicities of the new AML drug in different disease settings (e.g., solid tumor patients) and in healthy volunteers is helpful in ascertaining causality of adverse events.

- To assist with the adjudication of causality of fatal adverse events, the submission should include a data file with the date of death, study day of death, proximate cause of death (usually as reported by the investigator), and the root cause of death as determined by the sponsor. The root cause is generally categorized as a direct effect of active AML, an adverse reaction, or an unrelated intercurrent event (such as car accident). When the sponsor is considering additional categories for root cause, such as “early death,” feedback on the proposed categories should be sought at the presubmission meeting.

- For drugs with unusual adverse reactions, such as differentiation syndrome, FDA encourages sponsors to meet with FDA review staff prior to submission of a new drug

application (NDA) or biologics license application (BLA) to develop a detailed methodology for identifying cases, determine when additional narratives should be included in the submission, and to discuss the structure of the data files to be used for the analysis of such cases.

- When the study drug is used in multiple stages of AML treatment (e.g., in combination with induction, in combination with consolidation, and as maintenance), safety and laboratory data should be assessed by treatment stage.

- When a randomized trial has a comparator arm with a different duration of treatment (e.g., continuous oral therapy vs. a fixed duration of intensive salvage chemotherapy), it is important to compare toxicities between study arms for a similar duration of treatment. For long-term continuous treatment with investigational drug, safety beyond the period of comparison should be analyzed separately and compared to early-period toxicities to identify unique late-onset adverse reactions.

- For myelosuppressive AML drugs, an analysis should be performed to determine the incidence of prolonged thrombocytopenia (platelets < 50 Gi/L) or neutropenia (ANC < 0.5 Gi/L) past cycle day 42 in the absence of active leukemia.

3. Clinical Pharmacology

- If the AML drug is a CYP3A substrate, the submission should include analyses of the effect of concomitant drugs, including moderate and strong CYP3A inhibitors and inducers on the systemic exposure of parent drug and its active metabolites, on safety and efficacy, and whether the available safety and efficacy data support the proposed dose modifications for concomitant treatment with moderate and strong CYP3A inhibitors and inducers (see section III.A.3). If the AML drug or its major metabolite(s) is an inhibitor or inducer of metabolism enzymes or transporters, the submission should include analyses of the effect of the parent drug and major metabolites on the systemic exposure of concomitant drugs that are substrates of metabolism pathway or transporter and have a likelihood of coadministration (e.g., commonly-used antibiotics, other AML drugs in the combination regimen).

For submissions specifically for indications that target the population of patients with comorbidities that preclude use of intensive chemotherapy for AML, the submission should include the results of studies on the effects of renal and hepatic impairment on the systemic exposure of the parent drug and its active metabolites (see section III.A.3).

GLOSSARY

A. Terms referring to the types of AML treatment are defined as follows when used in this guidance

Episodic treatment: A treatment plan of multiple cycles of short-term administrations of intensive treatment. A typical course of episodic first-line treatment for AML consists of 1-2 cycles of induction and 2-4 cycles of consolidation with or without HSCT.

Continuous treatment: Repeated cycles of treatment, usually without a drug-free period. A typical course of continuous treatment of AML consists of daily dosing.

B. Terms referring to phases of AML treatment are defined as follows when used in this guidance

Induction: A limited course of treatment, usually intensive, with the objective of achieving CR.

Consolidation: A limited course of treatment, usually intensive, given after achievement of remission with the objective of reducing the risk of early relapse.

Maintenance: An extended but time-limited course of treatment, usually relatively nontoxic, given after achievement of CR with the objective of reducing the risk of relapse beyond the period of treatment. When the treatment plan allows for extended therapy for patients without achieving CR, the course is considered continued treatment rather than maintenance.

Continued treatment: An extended course of treatment after induction phase with the objective of controlling the AML disease burden while on therapy. Continued treatment may be time-limited, but it is generally administered until unacceptable toxicity or recurrence after a response.

C. Terms referring to intensities of AML treatment are defined as follows when used in this guidance

Intensive therapies: regimens expected to cause high-grade organ toxicity (including neurologic, pulmonary, cardiac, gastrointestinal, genitourinary, renal, hepatic, or cutaneous toxicities) or where the expected duration of neutropenia may approach 42 days from the start of the treatment cycle. Intensive regimens include 1-2 cycles of induction followed by consolidation with chemotherapy or HSCT.

Nonintensive therapies: lower doses of cytotoxic chemotherapy or targeted drugs with limited or no expected organ toxicities.

D. Disease status is assessed at the time of study enrollment. Terms relevant to AML disease status are defined as follows when used in this guidance

Primary refractory disease: The patient did not experience CR in response to first-line or any subsequent induction therapy.

Untreated relapse: The patient experienced CR in response to the last prior therapy, then demonstrated relapse and has not yet received definitive re-induction therapy for that relapse.

Refractory relapse: The patient experienced disease remission in response to past therapy, then demonstrated relapse and was treated with definitive re-induction therapy but did not experience CR with this re-induction.

Line of therapy: A line of therapy is defined as the planned therapy consisting of one or more cycles of episodic treatment or a defined period of continuous treatment. This may consist of single-agent or combination therapy as well as a planned sequence of treatment phases. For example, first-line treatment of AML with induction, consolidation, and allogeneic HSCT is considered one line of therapy. A line of therapy ends when the patient fails to achieve a response within a prespecified period (refractory) or relapses after achieving CR.

1162 **APPENDICES**

1163

1164 **Appendix 1: Example DLT Criteria for Drugs for AML**

Setting	Hematological SAR Criteria[a]	Nonhematological SAR Criteria
Healthy Volunteer Study	Any grade ≥ 2	Any grade ≥ 2
Continuous Long-Term Treatment (e.g., maintenance, extended treatments like imatinib)	Any grade ≥ 3 ANC or PLTS lasting more than 7 days	Any grade 3 lasting > 72 hours Any grade ≥ 4 Hy's law cases Any AR that leads to dose reduction or withdrawal
Short-Term Episodic Outpatient Therapy (e.g., CHOP-like)	Any grade ≥ 4 ANC or PLTS lasting more than 7 days	Any grade 3 (with exceptions) [b] Any grade ≥ 4 Hy's law cases Any AR that leads to dose reduction or withdrawal
Episodic Reduced Intensity (e.g., azacitidine)	Any grade ≥ 4 ANC or PLTS lasting past cycle day 28	Any grade 3 (with exceptions) [b] Any grade ≥ 4 Hy's law cases Any AR that leads to dose reduction or withdrawal
Episodic Intensive Chemotherapy with Curative Intent (e.g., 7+3 - based)	Any grade ≥ 4 ANC or PLTS lasting past cycle day 42	Grade ≥ 4 organ toxicity[c] Hy's law cases
CAR T Cells	Any grade ≥ 4 ANC or PLTS lasting past day 42, or marrow cellularity < 5% at day 42	Grade ≥ 3[d] CRS (with exceptions)[b] Grade 3 neurotoxicity (with exceptions)[b] Grade 4 neurotoxicity Other grade ≥ 3 toxicity to vital organs (with exceptions)[b,c]
Myeloablative Preparative Regimen (e.g., high-dose busulfan)	No ANC recovery to > 0.5 Gi/L by day 21 (PBSC), 28 (marrow), or 42 (UCBT)	Grade ≥ 4 organ toxicity[c]

Abbreviations: ANC - absolute neutrophil count, AR – adverse reaction, CAR - chimeric antigen receptor, CRS - cytokine release syndrome, PBSC - peripheral blood stem cells, PLTS - platelet count, SAR - suspected adverse reaction, and UCBT - umbilical cord blood transplantation.

[a] Not applicable in the presence of active leukemia. Patients with active leukemia are not evaluable for a hematological DLT.
[b] May exclude grade 3 toxicities that resolve within a prespecified time frame (e.g., 72 hours).
[c] Adverse reactions involving neurologic, pulmonary, cardiac, gastrointestinal, genitourinary, renal, hepatic, or cutaneous systems.
[d] Refers to Lee Criteria for CRS. In the remainder of the table, grade number refers to NCI-CTCAE criteria.

1165

Appendix 2: Additional Statistical Discussion

Postrandomization HSCT Subsequent Poststudy Treatments

For AML trials, it is common for patients to receive subsequent anti-AML treatments post-randomization, which include HSCT and/or anti-AML drugs (not to be confused with concomitant therapies). As use of subsequent treatments is consistent with the practice of medicine, FDA recommends that the primary analysis of a time-to-event endpoint (e.g., OS, EFS) not censor for subsequent treatments.[1] This approach implies that HSCT and/or subsequent anti-AML treatments are viewed as part of the as-needed AML treatment regimen taken after the initial study drug and that the treatment effect is the result of both the study drug and the subsequent anti-AML treatment.

To help ensure that the treatment effect is interpretable, AML trials should be designed such that investigators are blinded to patients' assigned treatment. Regardless of the feasibility of blinding and as HSCT extends survival, rules or criteria should be clearly prespecified in the protocol prior to study initiation to determine how patients are to be selected for HSCT. In addition, where patients are still on study, follow-up of patients should continue even after initiation of subsequent treatments.

It has been suggested that the true treatment effect should be free from the influence of HSCT or subsequent treatments.[2] Under this approach, the treatment effect may be interpreted as the difference in the endpoint between patients who initiated the investigational drug and patients who initiated the control treatment if HSCT and/or subsequent anti-AML treatments had not been available, or if available, were withheld from patients. In settings where HSCT and/or subsequent treatments are integral to the practice of medicine, this approach to thinking about the treatment effect is currently not recommended for the primary analysis for the following reasons:

- First, it may not be possible to design a clinical trial to estimate this treatment effect if patients are provided HSCT or subsequent treatments as needed. This implies that this treatment effect can only be estimated by modeling, using causal inference methods developed for observational studies where the assumptions therein are difficult, if not impossible, to justify.

- Second, the clinical relevance of such an estimand is still an open question if it can never be realized in practice.

Plateauing Effect

Trials designed to cure AML often result in survival contours characterized by an initial drop followed by a plateauing effect after some time point post randomization. This is an example of nonproportional hazards. While the log-rank test is somewhat robust to nonproportionality, it

[1] See the draft treatment policy discussion in the draft ICH *E9(R1)*. When final, this guidance will represent the FDA's current thinking on this topic.

[2] For additional reference, see discussion on hypothetical strategies in draft ICH *E9(R1)*. When final, this guidance will represent the FDA's current thinking on this topic.

generally results in loss of power. Furthermore, nonproportionality can cause difficulty in describing the treatment effect. FDA is open to discussion about analyses based on other approaches, such as weighted Cox regression or other weighted methods, or summarizing the treatment effect using restricted mean survival time (RMST) or landmark survival analysis. Plans that use these alternative approaches should include:

- justification for what constitutes clinically meaningful difference,
- justification of design parameters, such as sample size and follow-up duration, based on this endpoint, and
- justification for the value of the threshold that will be used to calculate the RMST.

Appendix 3: Additional Data Files for Marketing Applications for AML Drugs

The following variables are recommended for custom data files to assist with endpoint adjudication

Variables That Assist Morphological Response Assessment

- Study identification number
- Site identification number
- Unique subject number
- Treatment arm
- Date of start of study drug
- Date of last study drug
- Study day of last study drug
- Date of last platelet transfusion
- Study day of last platelet transfusion
- Date of last RBC transfusion
- Study day of last RBC transfusion
- Date of CR*
- Study day of CR*
- Date of ANC used for CR response*
- Study day of ANC used for CR response*
- ANC used for CR response*
- Date of platelet count used for CR response*
- Study day of platelet count used for CR response*
- Platelet count used for CR response*
- Date of marrow used for CR response*
- Study day of marrow used for CR response*
- Marrow blasts percentage used for CR response*
- Date of assessment of Auer rods (yes/no) at CR response*
- Date of assessment of extramedullary disease for CR response*
- Study day of assessment of extramedullary disease for CR response*
- Absence of extramedullary disease (yes/no) at CR response*
- Date of relapse
- Study day of relapse
- Date of transplantation
- Study day of transplantation

* If CRh is an endpoint in the study, these measures should also be provided for CRh.

Variables That Assist the Transfusion Independence Assessment

- Study identification number
- Site identification number
- Unique subject number
- Treatment arm
- Date of start of study drug
- Date of last study drug
- Study day of last study drug
- RBC transfusion dependence at baseline (yes/no)
- Platelet transfusion dependence at baseline (yes/no)
- Transfusion dependence for either RBC or platelets at baseline (yes/no)
- RBC transfusion independence (TI) criteria met post baseline (yes/no)
- Platelet TI criteria met post baseline (yes/no)
- TI criteria met for both RBC and platelet transfusions post baseline (yes/no)
- Date of start of RBC TI
- Study day of start of RBC TI
- Date of end of RBC TI
- Duration of RBC TI post baseline
- Date of start of platelet TI
- Study day of start of platelet TI
- Date of end of platelet TI
- Duration of platelet TI post baseline
- Date of start of RBC and platelet TI
- Study day of start of RBC and platelet TI
- Date of end of RBC and platelet TI
- Duration of RBC and platelet TI post baseline
- Date of last contact
- Study day of last contact
- Status at last contact (alive and TI, alive and transfusion-dependent, dead, or lost)