

- Cortes et al. (235) in a study of CML, defined EFS as death from any cause, loss of complete hematologic response (CHR), loss of complete cytogenetic response, discontinuation of therapy for toxicity or lack of efficacy, or progression to AP or BP.
- Caballero et al. (236) in a study of CLL, defined EFS as disease progression or death, and patients who did not reach disease response (complete or partial remission).
- Ades et al. (237) in a study of APL, defined EFS as treatment failure, death in first CR, and relapse included as events. CR means complete remission, where there were separate definitions for hematologic CR and for molecular CR.
- Devine et al. (238) in a review of pediatric leukemias, defined EFS as occurrence of a major adverse clinical event such as failure to achieve remission, relapse, and death during remission.

Regarding the endpoint of time-to-event, or event-free-survival, Fleming (239) cautions that this sort of composite endpoint should not be configured too broadly. Where the endpoint of time-to-event is defined, for example as “progression of major symptoms,” and “death,” the value of this particular endpoint would be reduced by using a broader composite that also includes the event “discontinuation of treatment” or “exposure to rescue treatment.”

b. Endpoint of relapse-free interval

Another interesting endpoint used in leukemia clinical trials is relapse-free interval (RFI). The endpoint of RFI refers to the amount of time between complete response (CR) and relapse. Relapse-free interval (RFI) is an endpoint used in about 5% of all oncology clinical trials, where it is mainly used in clinical trials of leukemia, lymphoma, breast cancer, melanoma, and sarcoma (240).

A definition of relapse, in the context of acute myeloid leukemia, is provided by National Comprehensive Cancer Network (241). This definition is relapse following complete response is defined as reappearance of leukemic blasts in the peripheral blood or the finding of more than 5% blasts in the bone marrow, not attributable to another cause.

²³⁵ Cortes JE, Jones D, O'Brien S, et al. Results of dasatinib therapy in patients with early chronic-phase chronic myeloid leukemia. *J Clin Oncol*. 2010;28:398–404.

²³⁶ Caballero D, García-Marco JA, Martino R, et al. Allogeneic transplant with reduced intensity conditioning regimens may overcome the poor prognosis of B-cell chronic lymphocytic leukemia with unmutated immunoglobulin variable heavy-chain gene and chromosomal abnormalities (11q- and 17p-). *Clin Cancer Res*. 2005;11:7757–7763.

²³⁷ Adès L, Chevret S, Raffoux E, et al. Is cytarabine useful in the treatment of acute promyelocytic leukemia? Results of a randomized trial from the European Acute Promyelocytic Leukemia Group. *J Clin Oncol*. 2006;24:5703–5710.

²³⁸ Devine S, Dagher RN, Weiss KD, Santana VM. Good clinical practice and the conduct of clinical studies in pediatric oncology. *Pediatr Clin North Am*. 2008;55:187–209.

²³⁹ Fleming TR. Addressing missing data in clinical trials. *Ann Intern Med*. 2011;154:113–117.

²⁴⁰ Search of articles in *Journal of Clinical Oncology*, published between 1990 and 2011. The search was conducted on March 7, 2011.

²⁴¹ National Comprehensive Cancer Network. Clinical Practice Guidelines in Oncology. Acute Myeloid Leukemia. 2008;37 pages.