decades, it is easy to discover new anticancer drugs, but it becomes progressively more difficult to find a new anticancer drug that works significantly better than other recently available drugs.

Where a new drug is devised, but where it is not certain whether a significant difference will be found between the new drug and an active control, the trial design may shift its perspective. The shifted perspective takes the form of a noninferiority trial. The main goal of a noninferiority trial is to show that the study drug is not less effective than the active control.

A clinical trial on a study drug that shows noninferiority to the active control can provide marketing advantages to the study drug, for the following reasons. As summarized by Lesaffre (115), these advantages include:

- While the efficacy of the study drug may be merely noninferior to the active control drug, the study drug may have a far better safety profile
- The study drug may be easier to administer. An example of this is fingolimod (116,117), which is a pill for multiple sclerosis, in contrast to natalizumab, which is injected
- The study drug may be administered by a flexible schedule, while the active control may require a strict, disciplined schedule.

b. Add-On Design Active Control

With an add-on design, the study drug is administered in combination with a previously established drug, and the control group receives only the previously established drug (118). According to the ICH Guidelines, "[a]n add-on study is a placebo-controlled trial of a new agent conducted in people also receiving standard treatment. Such studies are particularly important when available treatment is known to decrease mortality or irreversible morbidity, and when a noninferiority trial with standard treatment as the active control cannot be carried out or would be difficult to interpret. It is common to study anticancer, antiepileptic, and heart failure drugs this way" (119). The FDA has recognized that add-on design clinical studies are common in clinical trials in oncology, heart failure, seizure disorders, and human immunodeficiency virus (120).

According to Roberts et al. (121), it may be easier to obtain regulatory approval for an anticancer drug when the trial uses an add-on design, writing that, "most agents with first-line indications are approved for use in combination (eg, irinotecan plus fluorouracil and leucovorin for first-line colon cancer)."

[115]Lesaffre E. Superiority, equivalence, and non-inferiority trials. Bull. N.Y.U. Hosp. Jt. Dis. 2008;66:150–4.

[116]Cohen JA, Barkhof F, Comi G, et al. Oral fingolimod or intramuscular interferon for relapsing multiple sclerosis. New Engl. J. Med. 2010;362:402–15.

[117]Kappos L, Radue EW, O'Connor P, et al. A placebo-controlled trial of oral fingolimod in relapsing multiple sclerosis. New Engl. J. Med. 2010;362:387–401.

[118]Daugherty CK, Ratain MJ, Emanuel EJ, Farrell AT, Schilsky RL. Ethical, scientific, and regulatory perspectives regarding the use of placebos in cancer clinical trials. J. Clin. Oncol. 2008;26:1371–8.

[119]ICH Harmonised Tripartite Guideline. Choice of control group and related issues in clinical trials E10. (Step 4 version, July 2000) 33 pp.

[120]U.S. Dept. Health and Human Services. Food and Drug Administration. Guidance for Industry. Non-inferiority clinical trials; March 2010.

[121]Roberts TG, Lynch TJ, Chabner BA. The phase III trial in the era of targeted therapy: unraveling the "go or no go" decision. J. Clin. Oncol. 2003;21:3683–95.