analysis of plasma oblimersen. Also, blood samples taken on these days were used for measuring the in vivo influence of oblimersen on expression of the Bcl gene in white blood cells. Morris et al. (108) also provide a schema with extensive markings showing days of laboratory tests.

IV. FURTHER CONCEPTS IN CLINICAL TRIAL DESIGN

Additional concepts in study design include:

- *Active control*
- *Add-on design active control*
- *Three-arm study*
- *Dose modification and dose discontinuation.*

a. Active Control

Clinical trials typically use an active control treatment, including clinical trials that test new drugs, new surgical methods, and new medical devices. Where an established therapy exists, and where the efficacy and safety of the established therapy is reasonably predictable or uniform, an active control might be the preferred clinical trial design. Consider the hypothetical where a new drug is compared with a placebo. Assume the new drug works better than the placebo. However, even if the new drug works better than the placebo, the results do not provide any direct information on whether the drug works better than the established therapy. This comparison can only be established in a clinical trial where one arm contains the study drug, and where a control arm contains an active control that is an established therapy.

Examples of active controls are disclosed in the schema appearing above, that is, in the clinical trials of Perez et al. (109), Untch et al. (110), Puhalla et al. (111), and Sekine et al. (112). The FDA has specifically warned investigators, in choosing a drug for the active control, to avoid using an active drug that is outmoded or that has been replaced by another drug (113).

Sobrero and Guglielmi (114) noted the phenomenon where, over the course of decades, clinical trials in oncology using an active control design, have produced diminishing returns. In other words, with the passing of

[108]Morris MJ, Huang D, Kelly WK, et al. Phase 1 trial of high-dose exogenous testosterone in patients with castration-resistant metastatic prostate cancer. Eur. Urol. 2009;56:237–44.

[109]Perez EA, Suman VJ, Davidson NE, et al. Cardiac safety analysis of doxorubicin and cyclophosphamide followed by paclitaxel with or without trastuzumab in the North Central Cancer Treatment Group N9831 adjuvant breast cancer trial. J. Clin. Oncol. 2008;26:1231–8.

[110]Untch M, Möbus V, Kuhn W, et al. Intensive dose-dense compared with conventionally scheduled preoperative chemotherapy for high-risk primary breast cancer. J. Clin. Oncol. 2009;27:2938–45.

[111]Puhalla S, Mrozek E, Young D, et al. Randomized phase II adjuvant trial of dose-dense docetaxel before or after doxorubicin plus cyclophosphamide in axillary node-positive breast cancer. J. Clin. Oncol. 2008;26:1691–7.

[112]Sekine I, Nishiwaki Y, Noda K, et al. Randomized phase II study of cisplatin, irinotecan and etoposide combinations administered weekly or every 4 weeks for extensive small-cell lung cancer (JCOG9902-DI). Ann. Oncol. 2003;14:709–14.

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

[114]Sobrero A, Guglielmi A. Current controversies in the adjuvant therapy of colon cancer. Ann. Oncol. 2004;15 (Suppl. 4):iv 39–41.