The clinical trial of Marshall et al. (88) is a dose-escalation study (Fig. 2.18). Dose-escalation studies are used in Phase I clinical trials, where the goal is to arrive at the dose that is likely to be most effective, without resulting in intolerable toxicity. In the words of the investigators, "[e]nrollment to successive dose cohorts could not occur until all patients at the previous dose had received the 4-week treatment without dose limiting toxicity (DLT)" (89). This was a single arm, dose-escalation study.

The study drugs were docetaxel and oblimersen. Oblimersen is in a class of compounds called reverse sense RNA. When administered in vitro to cultured cells, or when administered to an animal or human subject, oblimersen inhibits expression of the Blc-2 gene. Oblimersen is used in cancers where the tumor overexpresses the Bcl-gene.

The dose of docetaxel was fixed throughout the entire study. But the dose of oblimersen was increased, in the indicated steps, in successive groups (cohorts) of subjects. For each individual subject, the subject was only exposed to one particular dosage, and that particular subject was never treated subsequently with a higher dosage. In detail, 2 subjects were used for a dose of 5 mg/kg/day, then 4 subjects were used for the 7 mg/kg/day regimen, and finally, 4 subjects were used for the 9 mg/kg/day regimen.

For each of the three escalating doses, the following schedule was used. In other words, the following schedule was repeated three times. The notation "PK" indicates the days that blood samples were taken for chemical analysis of plasma oblimersen. Also, blood samples taken on these days were used for measuring the influence of the in vivo influence of oblimersen on expression of the Bcl-gene in white blood cells. Morris et al. (90) also provide a schema with extensive markings showing days of laboratory tests.

IV. FURTHER CONCEPTS IN STUDY DESIGN

The following provides additional concepts in study design, as indicated by the bullet points:

- Active control;
- Add-on design;
- Where active control drug is the same drug as study drug; and
- Three-arm study.

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

[88] Marshall J, Chen H, Yang D, et al. A phase I trial of a Bcl-2 antisense (G3139) and weekly docetaxel in patients with advanced breast cancer and other solid tumors. *Ann Oncol*. 2004;15:1274–1283.

[89] Marshall J, Chen H, Yang D, et al. A phase I trial of a Bcl-2 antisense (G3139) and weekly docetaxel in patients with advanced breast cancer and other solid tumors. *Ann Oncol*. 2004;15:1274–1283.

[90] 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;56:237–244.