Treatment was continued until **tumor progression**, at which point treatment was halted, or until **toxicity to the patient**, at which point treatment was halted. The dose that resulted in toxicity represented dose-limiting toxicity (DLT) and was used to define the maximally tolerated dose (MTD). All patients in the trial were victims of incurable cancer, and had already been treated for the incurable cancer. What is described above is standard procedure in the pharmaceutical industry.

The result of the Moore et al. (84) study was that the MTD was 800 mg sorafenib per day. The authors recommended that this dose be used for subsequent Phase II and Phase III trials. Van Cutsem et al. (85) provide a similar schema used for another dose-escalating trial.

t. Pharmacokinetics – the Marshall schema

The schema provided by Marshall et al. (86) is distinguished in that it indicates the time points relating to analytical methods (Fig. 2.18). The indicated time points are dates when blood was withdrawn. Blood samples were taken for use in the analysis of plasma drugs and drug metabolites, and for the characterization of the pharmacokinetic (PK) and pharmacodynamic (PD) properties of the drug. The term *pharmacodynamics* refers to the drug's influence on physiology, biochemistry, and molecular biology over the course of time.

Although most clinical trials include an analysis of pharmacokinetics, the Marshall et al. (87) schema is one of the few that indicate dates of blood collection.

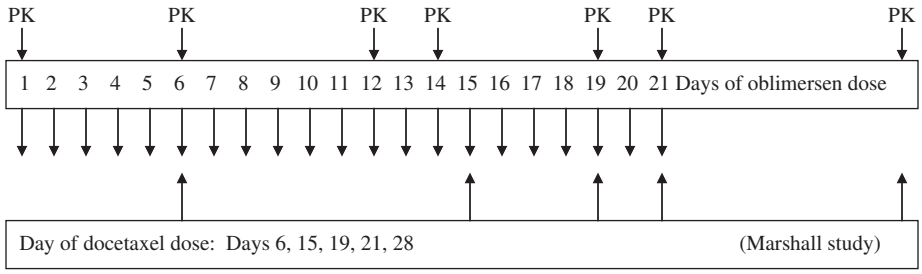

Figure 2.18 Study schema showing time points for withdrawing blood. Blood was withdrawn from study subjects at the time points indicated by arrows, to characterize the pharmacokinetic and pharmacodynamic properties of the drug

[84] Moore M, Hirte HW, Siu L, et al. Phase I study to determine the safety and pharmacokinetics of the novel Raf kinase and VEGFR inhibitor BAY 43-9006, administered for 28 days on/7 days off in patients with advanced, refractory solid tumors. *Ann Oncol*. 2005;16:1688–1694.

[85] Van Cutsem E, Verslype C, Beale P, et al. A phase Ib dose-escalation study of erlotinib, capecitabine and oxaliplatin in metastatic colorectal cancer patients. *Ann Oncol*. 2008;19:332–339.

[86] 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.

[87] 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.