In an article on renal cancer, Rosner et al. (42) used the term *randomized discontinuation design*, to refer to a trial that contains a run-in period, where the run-in period selects a subset of enrolled patients who are relatively homogeneous with respect to important prognostic factors and where the trial randomizes only these patients. This kind of run-in period takes the form of a short clinical trial, where efficacy is measured, and where only subjects who respond with predetermined criteria are kept in the study, and subsequently randomized to the study drug and control. Chow and Chang (43) called the above described trial design a *drop-the-losers design*.

In a study of melanoma treatment with sorafenib, Eisen et al. (44) used a run-in period (12 weeks) as a miniature clinical trial, in order to assess the response to the study drug. What was assessed was the response of the tumors to the drug. Where the tumor grew at a rapid rate during the run-in period, subjects were not included in the trial. Where there was a dramatic reduction in tumor size, subjects were also not included. Only subjects with an in-between response were used for the trial where, after the run-in, subjects were divided into the study drug group and the placebo group. The subjects who actually entered the trial were, "[t]hose patients who had an unconfirmed change in tumour size of <25% were randomised in a double-blind fashion to receive either sorafenib...or matching placebo from week 12 onwards." Ratain et al. (45) described this 12-week run-in period, as well as other details of the same melanoma study.

l. Methodology Tip—Anticancer Drugs That Inhibit Tumor Growth and Merely Stabilize Tumors

A review by Stadler (46) focuses on a type of response where a drug stabilizes tumor size, that is, where the effect of the drug is maintenance of tumor size, and not tumor shrinkage. The endpoint of tumor stabilization is preferred where the mechanism of action of the drug is inhibiting tumor cell growth, not killing tumors. Sorafenib is one such drug. Anticancer drugs that halt angiogenesis tend not to kill tumors, but instead merely inhibit tumor growth. Ma and Waxman (47) provide a review of about a dozen antiangiogenic drugs, including sorafenib. These authors expressly state that, "anti-angiogenics are generally cytostatic rather than cytoreductive."

m. Decision Tree

A run-in period can be used to create a branching point, where investigators determine whether the subject should receive treatment A or treatment B. In a clinical trial of head and

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