the study, and subsequently randomized to the study drug and control. Chow and Chang (42) called the above-described trial design a drop-the-losers design.

In a study of melanoma treatment with sorafenib, Eisen et al. (43) used a run-in period (12 weeks) as a miniature clinical trial in order to assess 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. (44) described this 12-week run-in period, as well as other details of the same melanoma study.

## l. Methodology tip – anti-cancer drugs that inhibit tumor growth

A review by Stadler (45) 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. Anti-cancer drugs that halt angiogenesis tend not to kill tumors, but instead merely inhibit tumor growth. Ma and Waxman (46) provide a review of about a dozen anti-angiogenic 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 if the subject should receive treatment A or treatment B. In a clinical trial of head and neck cancer by Worden et al. (47,48) subjects were first treated with one cycle of

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[44] Ratain MJ, Eisen T, Stadler WM, et al. Phase II placebo-controlled randomized discontinuation trial of sorafenib in patients with metastatic renal cell carcinoma. *J Clin Oncol*. 2006;24:2505–2512.

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[46] Ma J, Waxman DJ. Combination of antiangiogenesis with chemotherapy for more effective cancer treatment. *Mol Cancer Ther*. 2008;7:3670–3684.

[47] Worden FP, Kumar B, Lee JS. Chemoselection as a strategy for organ preservation in advanced oropharynx cancer: response and survival positively associated with HPV16 copy number. *J Clin Oncol*. 2008;26:3138–3146.

[48] Prof. Warden agreed with the author's perception that this approach can be classified as a run-in period. E-mail of August 2, 2010.