The hazard ratio (HR) in comparing drug versus placebo was HR = 0.45 where the tumors had wild-type, nonmutated *KRAS*. The HR in comparing drug versus placebo was HR = 0.99, where tumors had mutated *KRAS*.

In view of results such as these, the American Society of Clinical Oncology (ASCO), recommended that only patients with wild-type *KRAS* be treated with anti-EGFR therapy, and that patients with mutated *KRAS* should not receive this treatment (21,22). In this chapter, mutated *KRAS* refers to mutations at codons 12 or 13.

To summarize, colorectal cancer patients with *KRAS* mutations face two types of bad news. The first bad news is that these mutations are prognostic for worse outcome. The second type of bad news is that anti-EGFR is not recommended, where the cancer expresses *KRAS* that is mutated at codons 12 or 13.

b. Including Biomarker Tests in the Study Design

Biomarker status can be an integral part of trial design, that is, for dictating the nature of the study schema. As indicated by three study schema, shown below, biomarker status can be used: (1) to serve as an inclusion or exclusion criterion (Fig. 19.1); (2) to stratify subjects (Fig. 19.2); and (3) to dictate the treatment, for example, drug A versus drug B (Fig. 19.3) (23).

c. Criteria for Surrogates

The following concerns surrogate markers, as well as markers that do not meet the stringent requirements for a marker to be considered a surrogate marker. According to the Prentice criteria (24,25), a valid surrogate is one that correlates with the true clinical outcome and fully captures the net effect of drug treatment. The term *surrogate* refers to a biological parameter, such as tumor shrinkage, cholesterol levels, blood pressure, bloodstream virus levels, or serum levels of a tumor antigen, where the measured value can replace the true clinical outcome, and contribute to convincing a regulatory agency to approve the study drug. Regarding these particular examples, tumor shrinkage can be a surrogate for

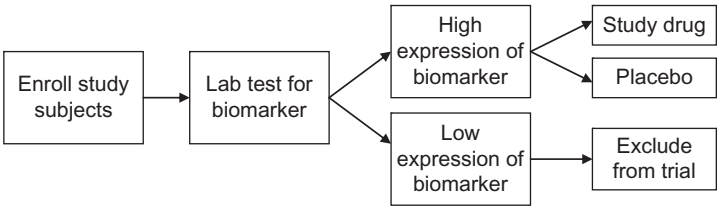

FIGURE 19.1 Biomarkers can be used when determining inclusion criteria or exclusion criteria.

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