

IV. CONCLUDING REMARKS

Biomarkers can be a basis for the stratification of study subjects. They can be used in a decision tree residing in the schema of a clinical trial. Or they can be used purely for exploratory purposes. Changes in expression of a biomarker, during the course of medical treatment, can be used to determine if any given patient is a high-risk or low-risk patient. Biomarkers can also determine if a particular drug will likely work for any given patient.

Regarding the studies described above, the Vogel study (135) showed that HER2 can predict a drug's efficacy. The Cohen study (136) showed that circulating tumor cells can be used as a biomarker to predict survival time. The Koelink study (137) showed that a tumor protein found in the bloodstream, cytokeratin, can predict survival time. The Galon study (138,139) concerned a biomarker that took the form of immune cells clustering around a tumor, where the goal of using this biomarker was to predict survival. The Morris study (140) also involved immune cells, and here the goal was to predict if a drug would be effective. This chapter also discloses use of gene arrays as a biomarker. Gene arrays are distinguished in that no single particular gene has a reliable prognostic value, but that a large collection of genes, having various unrelated functions (or even having unknown functions), can be used as a biomarker.

Although this textbook focuses mainly on oncology, C-reactive protein (CRP), which is mainly used as a biomarker for atherosclerosis, was also detailed above. CRP was detailed for a variety of reasons. First, there has been an increasing interest in using CRP as a biomarker for oncology. Second, the utility of CRP for oncology as well as for atherosclerosis provides an excellent teaching example regarding the principles set forth by Fleming and DeMets (141). It can be concluded that CRP is reasonable to use as an exploratory biomarker, suitable to use as an inclusion/exclusion criterion, reasonable to use as a basis for stratifying subjects into subgroups, and suitable for use in the clinic as a prognostic marker. However, in view of the lack of evidence that

¹³⁵ Vogel CL, Cobleigh MA, Tripathy D, et al. Efficacy and safety of trastuzumab as a single agent in first-line treatment of HER2-overexpressing metastatic breast cancer. *J Clin Oncol.* 2002;20:719–726.

¹³⁶ Cohen SJ, Punt CJ, Iannotti N, Savidman BH, et al. Relationship of circulating tumor cells to tumor response, progression-free survival, and overall survival in patients with metastatic colorectal cancer. *J Clin Oncol.* 2008;26:3213–3221.

¹³⁷ Koelink PJ, Lamers CB, Hommes DW, Verspaget HW. Circulating cell death products predict clinical outcome of colorectal cancer patients. *BMC Cancer.* 2009;9:88.

¹³⁸ Galon J, Costes A, Sanchez-Cabo F, et al. Type, density, and location of immune cells within human colorectal tumors predict clinical outcome. *Science.* 2006;313:1960–1964.

¹³⁹ Couzin J. T cells a boon for colon cancer prognosis. *Science.* 2006;313:1868–1869.

¹⁴⁰ Morris M, Platell C, Iacopetta B. Tumor-infiltrating lymphocytes and perforation in colon cancer predict positive response to 5-fluorouracil chemotherapy. *Clin Cancer Res.* 2008;14:1413–1417.

¹⁴¹ Fleming TR, DeMets DL. Surrogate end points in clinical trials: are we being misled? *Ann Intern Med.* 1996;125:605–613.