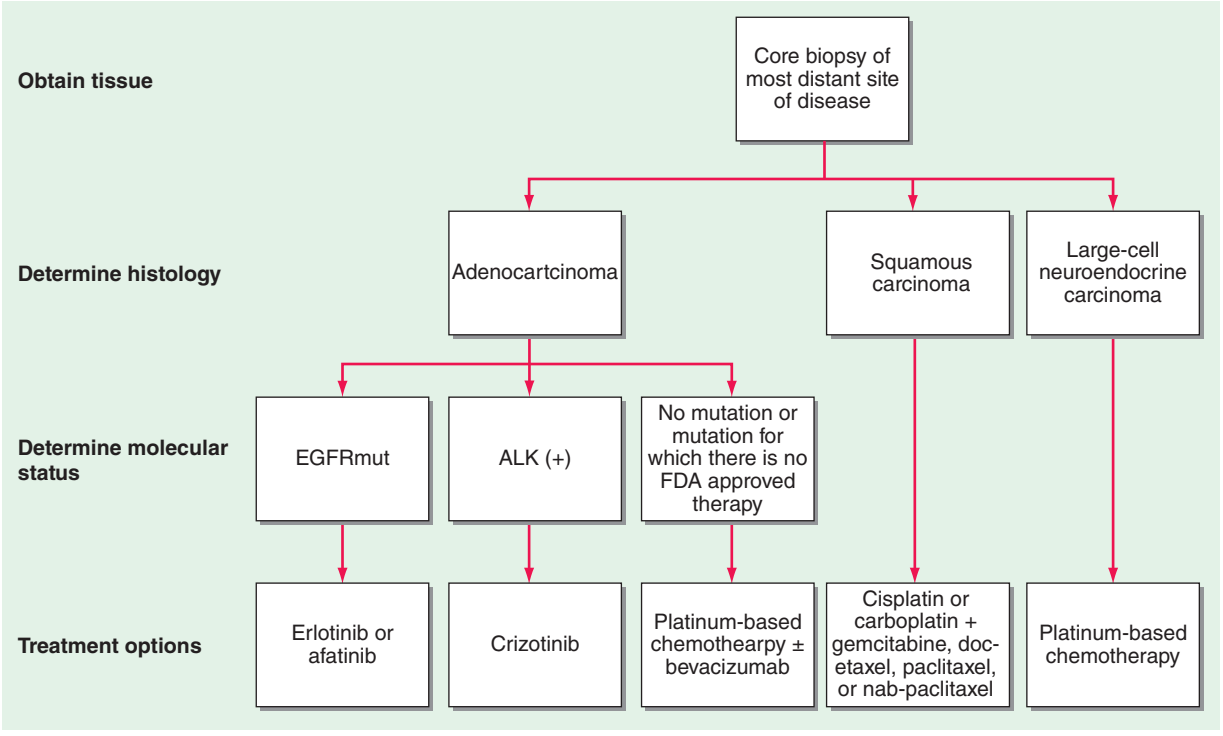

FIGURE 107-8 Approach to first-line therapy in a patient with stage IV non-small-cell lung cancer (NSCLC). EGFRmut, *EGFR* mutation; FDA, Food and Drug Administration.

targeted inhibitors based specifically on the tumor's molecular profile. Furthermore, increased understanding of how to activate the immune system to drive antitumor immunity is proving to be a promising therapeutic strategy for some patients with advanced lung cancer. In Fig. 107-8, we propose an algorithm of the treatment approach for patient with stage IV NSCLC. However, the reality is that the majority of patients treated with targeted therapies or chemotherapy eventually develop resistance, which provides strong motivation for further research and enrollment of patients onto clinical trials in this rapidly evolving area.

108 Breast Cancer

Marc E. Lippman

Breast cancer is a malignant proliferation of epithelial cells lining the ducts or lobules of the breast. In the year 2014, about 180,000 cases of invasive breast cancer and 40,000 deaths will occur in the United States. In addition, about 2000 men will be diagnosed with breast cancer. Epithelial malignancies of the breast are the most common cause of cancer in women (excluding skin cancer), accounting for about one-third of all cancer in women. As a result of improved treatment and earlier detection, the mortality rate from breast cancer has begun to decrease very substantially in the United States. This Chapter will not consider rare malignancies presenting in the breast, such as sarcomas and lymphomas, but will focus on the epithelial cancers.

GENETIC CONSIDERATIONS

Human breast cancer is a clonal disease; a single transformed cell—the product of a series of somatic (acquired) or germline mutations—is eventually able to express full malignant potential. Thus, breast cancer may exist for a long period as either a noninvasive disease or an invasive but nonmetastatic disease. These facts have significant clinical ramifications.

Not more than 10% of human breast cancers can be linked directly to germline mutations. Several genes have been implicated in familial cases. The Li-Fraumeni syndrome is characterized by inherited mutations in the *p53* tumor-suppressor gene, which lead to an increased incidence of breast cancer, osteogenic sarcomas, and other malignancies. Inherited mutations in *PTEN* have also been reported in breast cancer.

Another tumor-suppressor gene, *BRCA1*, has been identified at the chromosomal locus 17q21; this gene encodes a zinc finger protein, and the protein product functions as a transcription factor and is involved in gene repair. Women who inherit a mutated allele of this gene from either parent have at least a 60–80% lifetime chance of developing breast cancer and about a 33% chance of developing ovarian cancer. The risk is higher among women born after 1940, presumably due to promotional effects of hormonal factors. Men who carry a mutant allele of the gene have an increased incidence of prostate cancer and breast cancer. A fourth gene, termed *BRCA2*, which has been localized to chromosome 13q12, is also associated with an increased incidence of breast cancer in men and women.

Germline mutations in *BRCA1* and *BRCA2* can be readily detected; patients with these mutations should be counseled appropriately. All women with strong family histories for breast cancer should be referred to genetic screening programs, particularly women of Ashkenazi Jewish descent who have a high likelihood of a specific founder *BRCA1* mutation (substitution of adenine for guanine at position 185).

Even more important than the role these genes play in inherited forms of breast cancer may be their role in sporadic breast cancer. A *p53* mutation is present in nearly 40% of human breast cancers as an acquired defect. Acquired mutations in *PTEN* occur in about 10% of the cases. *BRCA1* mutation in sporadic primary breast cancer has not been reported. However, decreased expression of *BRCA1* mRNA (possibly via gene methylation) and abnormal cellular location of the BRCA1 protein have been found in some breast cancers. Loss of heterozygosity of *BRCA1* and *BRCA2* suggests that tumor-suppressor