of antagonists from mutant steroid hormone receptors that have come to depend on the presence of the antagonist as a growth-promoting influence.

Additional strategies to treat refractory breast and prostate cancers that possess steroid hormone receptors may also address adrenal capacity to produce androgens and estrogens, even after orchiectomy or oophorectomy, respectively. Thus, aminoglutethimide or ketoconazole can be used to block adrenal synthesis by interfering with the enzymes of steroid hormone metabolism. Administration of these agents requires concomitant hydrocortisone replacement and additional glucocorticoid doses administered in the event of physiologic stress.

Humoral mechanisms can also result in complications from an underlying malignancy producing the hormone. Adrenocortical carcinomas can cause Cushing's syndrome as well as syndromes of androgen or estrogen excess. Mitotane can counteract these by decreasing synthesis of steroid hormones. Islet cell neoplasms can cause debilitating diarrhea, treated with the somatostatin analogue octreotide. Prolactin-secreting tumors can be effectively managed by the dopaminergic agonist bromocriptine.

DIAGNOSTICALLY GUIDED THERAPY The basis for discovery of drugs of this type was the prior knowledge of the importance of the drugs' molecular target to drive tumors in different contexts. Figure 103e-4 summarizes how FDA-approved targeted agents act. In the case of diagnostically guided targeted chemotherapy, prior demonstration of a specific target is necessary to guide the rational use of the agent, while in the case of targeted agents directed at oncogenic pathways, specific diagnosis of pathway activation is not yet necessary or in some cases feasible, although this is an area of ongoing clinical research. Table 103e-5 lists currently approved targeted chemotherapy agents, with features of their use.

In hematologic tumors, the prototypic agent of this type is imatinib, which targets the ATP binding site of the $p210^{bcr\text{-}abl}$ protein tyrosine kinase that is formed as the result of the chromosome 9;22 translocation producing the Philadelphia chromosome in CML. Imatinib is superior to interferon plus chemotherapy in the initial treatment of the chronic phase of this disorder. It has lesser activity in the blast phase of CML, where the cells may have acquired additional mutations in $p210^{bcr\text{-}abl}$ itself or other genetic lesions. Its side effects are relatively tolerable in most patients and include hepatic dysfunction, diarrhea, and fluid retention. Rarely, patients receiving imatinib have decreased cardiac function, which may persist after discontinuation of the drug. The quality of response to imatinib enters into the decision about when to refer patients with CML for consideration of transplant approaches. Nilotinib is a tyrosine protein kinase inhibitor with a similar spectrum of activity to imatinib, but with increased potency and perhaps better tolerance by certain patients. Dasatinib, another inhibitor of the $p210^{bcr\text{-}abl}$ oncoproteins, is active in certain mutant variants of $p210^{bcr\text{-}abl}$ that are refractory to imatinib and arise during therapy with imatinib or are present de novo. Dasatinib also has inhibitory action against kinases belonging to the src tyrosine protein kinase family; this activity may contribute to its effects in hematopoietic tumors and suggest a role in solid tumors where src kinases are active. The T315I mutant of $p210^{bcr\text{-}abl}$ is resistant to imatinib, nilotinib, bosutinib, and dasatinib; ponatinib has activity in patients with this $p210^{bcr\text{-}abl}$ variant, but ponatinib has noteworthy associated thromboembolic toxicity. Use of this class of targeted agents is thus critically guided not only by the presence of the $p210^{bcr\text{-}abl}$ tyrosine kinase, but also by the presence of different mutations in the ATP binding site.

All-*trans*-retinoic acid (ATRA) targets the PML-retinoic acid receptor (RAR) α fusion protein, which is the result of the chromosome 15;17 translocation pathogenic for most forms of APL. Administered orally, it causes differentiation of the neoplastic promyelocytes to mature granulocytes and attenuates the rate of hemorrhagic complications. Adverse effects include headache with or without pseudotumor cerebri and gastrointestinal and cutaneous toxicities.

In epithelial solid tumors, the small-molecule epidermal growth factor (EGF) antagonists act at the ATP binding site of the EGF receptor tyrosine kinase. In early clinical trials, gefitinib showed evidence of responses in a small fraction of patients with non-small-cell lung cancer (NSCLC). Side effects were generally acceptable, consisting mostly of rash and diarrhea. Subsequent analysis of responding patients revealed a high frequency of activating mutations in the EGF receptor. Patients with such activating mutations who initially responded to gefitinib but who then had progression of the disease then acquired additional mutations in the enzyme, analogous functionally to mutational variants responsible for imatinib resistance in CML. Erlotinib is another EGF receptor tyrosine kinase antagonist with a superior outcome in clinical

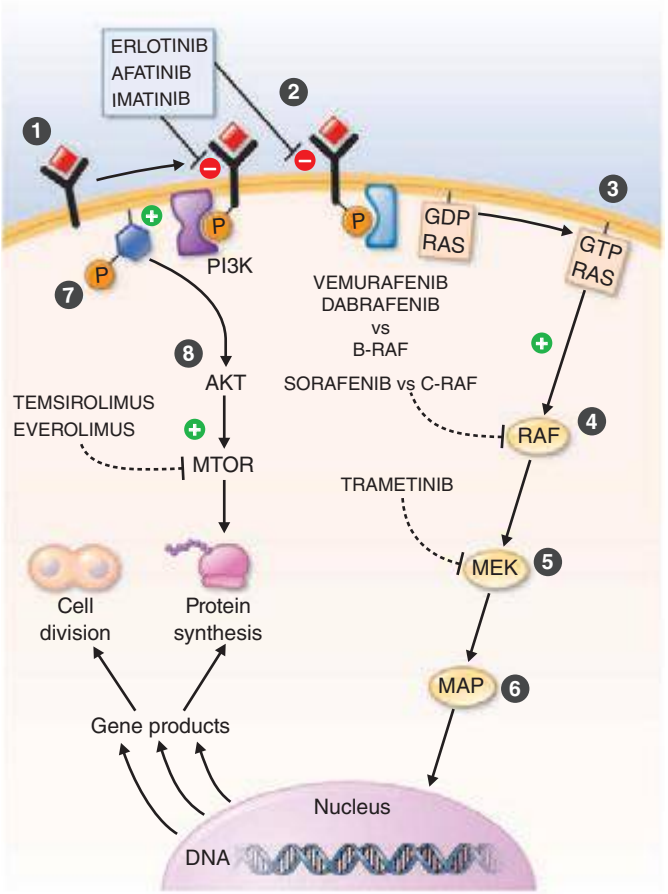

FIGURE 103e-4 Targeted chemotherapeutic agents act in most instances by interrupting cell growth factor-mediated signaling pathways. After a growth factor binds to is cognate receptor (1), in many cases there is activation of tyrsosine kinase activity particularly after dimerization of the receptors (2). This leads to autophosphorylation of the receptor and docking of "adaptor" proteins. One important pathway activated occurs after exchange of GDP for GTP in the RAS family of proto-oncogene products (3). GTP-RAS activates the RAF proto-oncogene kinase (4), leading to a phosphorylation cascade of kinases (5, 6) that ultimately impart signals to regulators of gene function to produce transcripts which activate cell cycle progression and increase protein synthesis. In parallel, tyrosine phosphorylated receptors can activate the phosphatidylinositol-3-kinase to produce the phosphorylated lipid phosphatidyl-inositol-3- phosphate (7). This leads to the activation of the AKT kinase(8) which in turn stimulates the mammalian "Target of Rapamycin" kinase (mTOR), which directly increases the translation of key mRNAs for gene products regulating cell growth. Erlotinib and afatinib, are examples of Epidermal Growth Factor receptor tyrosine kinase inhibitors; imatinib can act on the nonreceptor tyrosine kinase bcr-abl or c-KIT membrane bound tyrosine kinase. Vemurafenib and Dabrafenib act on the B isoform of RAF uniquely in melanoma, and c-RAF is inhibited by sorafenib. Trametinib acts on MEK. Temsirolimus and everolimus inhibit mTOR kinase to downregulate translation of oncogenic mRNAs.