PI3K/AKT pathway have been found in various cancers, but as with the RAS/MAPK pathway, the factors at the top of the pathway, PI3K and its antagonist, PTEN, are most frequently mutated. PI3K mutations affect the catalytic subunits and generally result in an increase in enzyme activity. For example, about 30% of breast carcinomas have gain-of-function mutations involving the α-isoform of the PI3K catalytic subunit. As would be expected, *PTEN* is a tumor suppressor gene whose function is lost through mutation or epigenetic silencing in many cancers, particularly endometrial carcinomas (Chapter 21).

Because RAS proteins are so frequently mutated in human cancers, much effort has been spent to develop targeted therapy specific for these proteins. Unfortunately, none of the strategies designed to target RAS has so far been successful, in part because the vagaries of RAS protein structure and its mode of signaling make it a particularly difficult protein to inhibit with drugs. In contrast, treatment of patients with advanced melanomas harboring activating BRAF mutations with BRAF inhibitors have produced striking clinical responses. Such responses are strictly restricted to tumors with BRAF mutations, as morphologically identical melanomas without BRAF mutations never respond to BRAF inhibitors. This phenomenon, termed oncogene addiction (described below), highlights the need for molecular analysis to guide appropriate therapy. Multiple drugs that inhibit various PI3K isoforms have also been developed and are now being tested in the clinic.

Alterations in Nonreceptor Tyrosine Kinases. Mutations that confer oncogenic activity occur in several nonreceptor tyrosine kinases that normally localize to the cytoplasm or the nucleus. In many instances the mutations take the form of chromosomal translocations or rearrangements that create fusion genes encoding constitutively active tyrosine kinases. Despite their nonmembranous localization, most of these oncoproteins also activate the same signaling pathways as receptor tyrosine kinases. An important example of this oncogenic mechanism involves the ABL tyrosine kinase. In *chronic myelogenous leukemia* (CML) and some *acute lymphoblastic leukemias*, the *ABL* gene is translocated from its normal abode on chromosome 9 to chromosome 22 (Fig. 7-26), where it fuses with the *BCR* gene (see discussion of chromosomal translocations later in this chapter). The resultant chimeric gene encodes a constitutively active, oncogenic *BCR-ABL tyrosine kinase*. The most important contribution of the BCR moiety is that it promotes self-association of BCR-ABL, which appears to be sufficient to unleash tyrosine kinase activity of ABL. This is a recurrent mechanism in cancer, in that many different oncogenic tyrosine kinases consist of fusion proteins in which the non-tyrosine kinase partner drives self-association.

Treatment of CML has been revolutionized by the development of "designer" drugs with low toxicity and high therapeutic efficacy that inhibit the BCR-ABL kinase, another example of rational drug design emerging from an understanding of the molecular basis of cancer. The remarkable therapeutic response of CML to BCR-ABL inhibitors is one of the first and best examples of *oncogene addiction*, in which tumor cells are highly dependent on the activity of one or more oncogenes. Despite accumulation of mutations in other cancer-associated genes in CML cells, signaling through the BCR-ABL tyrosine kinase is required for most CML tumor cells to proliferate and survive, hence inhibition of its activity is a highly effective therapy. The presence of a *BCR-ABL* fusion gene defines CML and must be the initiating event in this disease; thus, additional mutations acquired by the founding clone are selected for their ability to complement the effects of constant signaling through BCR-ABL. BCR-ABL signaling can be seen as the central lodgepole around which a complex oncogenic structure is built. If the lodgepole is removed by inhibition of the BCR-ABL kinase, the entire structure collapses. Unfortunately, treatment of this "addiction" with BCR-ABL inhibitors does not lead to cure. Even though the proliferating component of the tumor is suppressed by BCR-ABL inhibitors and the patient seems completely well, rare CML "stem cells" harboring the *BCR-ABL* fusion gene persist, apparently because these cells do not require BCR-ABL signals for their survival. As a result, therapy with BCR-ABL inhibitors must be continued indefinitely;

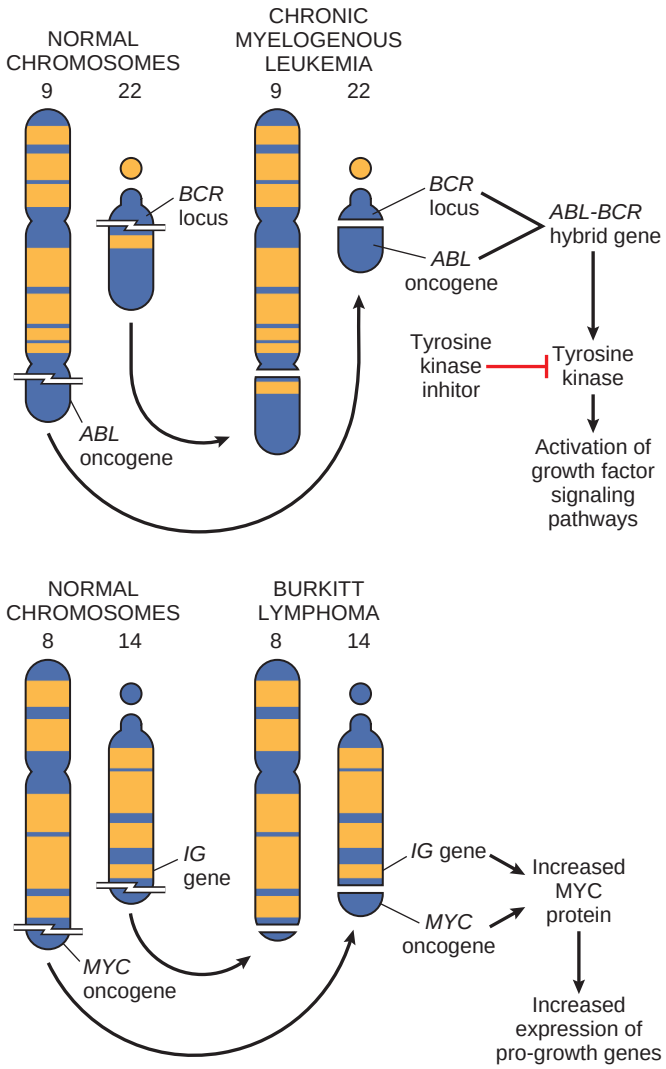

Figure 7-26 The chromosomal translocation and associated oncogenes in Burkitt lymphoma and chronic myelogenous leukemia.