of the BCR/ABL1 fusion gene, followed by a second translocation that restores what appears to be the original, normal chromosomes. Virgili et al. (182) have identified the locations of the BCR/ABL1 fusion gene in a number of Ph-negative CML patients.

In addition to t(9;22)(q34;q11), that is, the Philadelphia chromosome, Brazma, et al. (183) and Nacheva et al. (184) have identified a number of chromosomal abnormalities in CML, where these abnormalities occur, for example, at 1p36, 5q21, 7p12, 8q24, 9p21, 9q34, 9q34, 14q11, 14q32, and 22q11. Moreover, a variety of gene mutations have been associated with CML, most notably affecting CDKN2A/2B, EVI-1, RB, MYC, and p53 genes (185). The possibility that these chromosomal abnormalities and genetic mutations contribute to the progression of CML, or can be used as a prognostic marker, is currently being explored. The following concerns the time point for conducting an analysis of chromosomal aberrations and gene mutations. Evidence suggests that the BCR/ABL1 fusion protein itself can induce the accumulation of additional genetic lesions, including point mutations, gene amplifications, genome loss and chromosome translocations, and that these mutations drive the malignant process (186).

d. Utility of the Philadelphia chromosome in diagnosis, drug target, and for assessing response

The following genetic marker finds utility as a diagnostic marker, drug target, and prognostic factor. In short, the Philadelphia chromosome, or its expressed mRNA and polypeptide, can be used as follows:

- Diagnosing leukemia
- As a target of kinase inhibitors
- To measure objective response to chemotherapy, for example, in the minimal residual disease (MRD) assay (187,188,189)

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