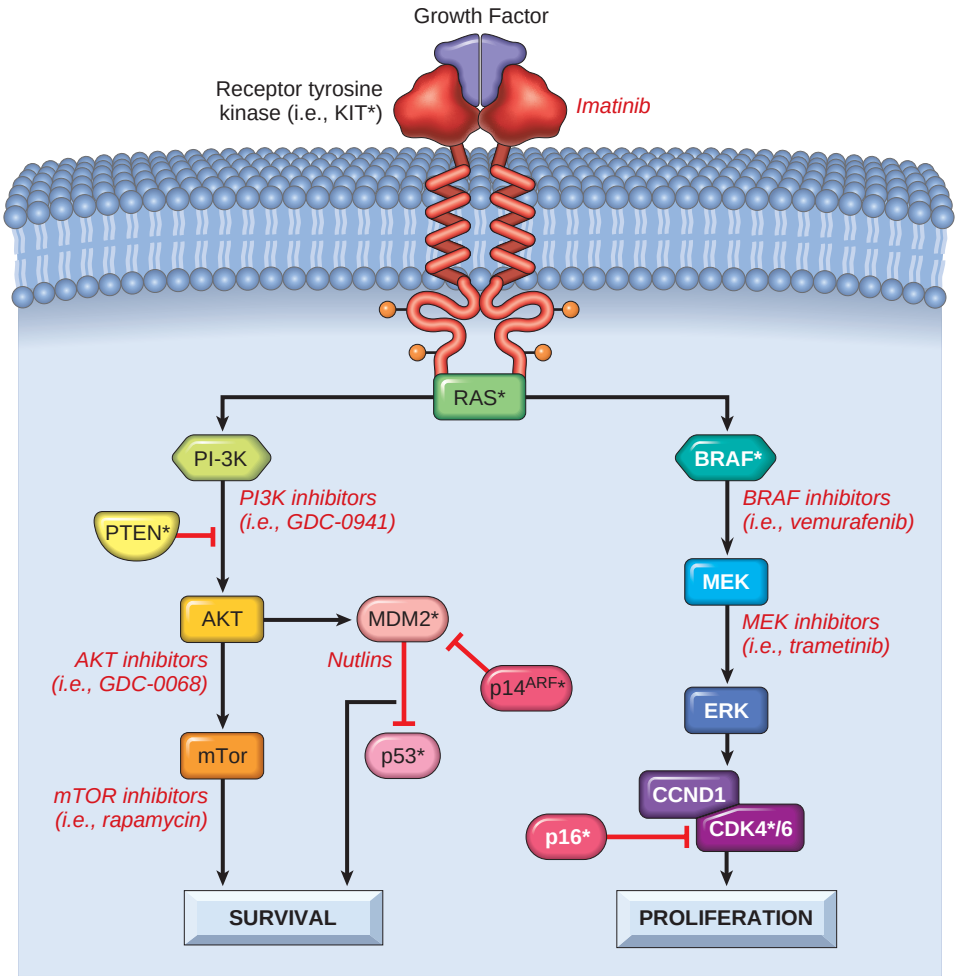

Figure 25-7 Pathways important in melanoma. Growth factors activate signaling circuits involving receptor tyrosine kinases (e.g., KIT), RAS, and two key downstream pathways that include the serine/threonine kinase BRAF and the phospholipid kinase PI3K. Proteins indicated by asterisks are mutated in melanoma. Components of these pathways that are being targeted by drugs are indicated.

autosomal dominant familial melanoma. *CDKN2A* is a complex locus that encodes three different tumor suppressors, p15/INK4b, p16/INK4a, and p14/ARF. Of these, loss of p16/INK4a is clearly implicated in human melanoma, and experimental evidence also supports a role for loss of p14/ARF. As already mentioned, p16/INK4a inhibits cyclin-dependent kinase 4 (CDK4) and cyclin-dependent kinase 6 (CDK6), thus reinforcing the ability of the RB tumor suppressor to block cells in the G_1 phase of the cell cycle. By contrast, p14/ARF enhances the activity of the p53 tumor suppressor by inhibiting MDM2, an oncoprotein that stimulates p53 degradation. *CDKN2A* is mutated in approximately 10% of sporadic melanomas, and these mutations uniformly abolish the production of p16/INK4a and more variably affect p14/ARF. However, it is suspected that these mutations are the tip of the "oncogenic iceberg" with respect to molecular lesions affecting the G_1 checkpoint. For example, 30% to 70% of melanomas show loss of p16/INK4a expression though varied mechanisms, and other familial and sporadic melanomas have mutations in CDK4 that prevent its inhibition by p16/INK4a. The net effect of all of these alterations is the same; increased melanocytic proliferation due to loss of cell-cycle control and escape from oncogene-induced cellular senescence.

- *Mutations that activate pro-growth signaling pathways.* A second common group of molecular lesions in sporadic melanoma leads to aberrant increases in RAS and PI3K/AKT signaling (Fig. 25-7), which you will recall promote cell growth and survival (Chapter 7). Activating mutations in BRAF, a serine/threonine kinase that is downstream of RAS, are seen in 40% to 50% of melanomas, while activating mutations in NRAS occur in an additional 15% to 20% of tumors. Melanomas with BRAF mutations also often show loss of the PTEN tumor suppressor, leading to heightened activation of the PI3K/AKT pathway. For reasons that are unclear, melanomas arising in non-sun exposed cutaneous sites rarely have mutations in BRAF or NRAS and are more likely to have activating mutations in the receptor tyrosine kinase KIT, which sits upstream of both RAS and PI3K/AKT. PTEN is also silenced in 20% of melanomas arising at in non-sun exposed sites. Other melanomas have loss-of-function mutations in the tumor suppressor neurofibromin 1 (NF1), a negative regulator of RAS, which