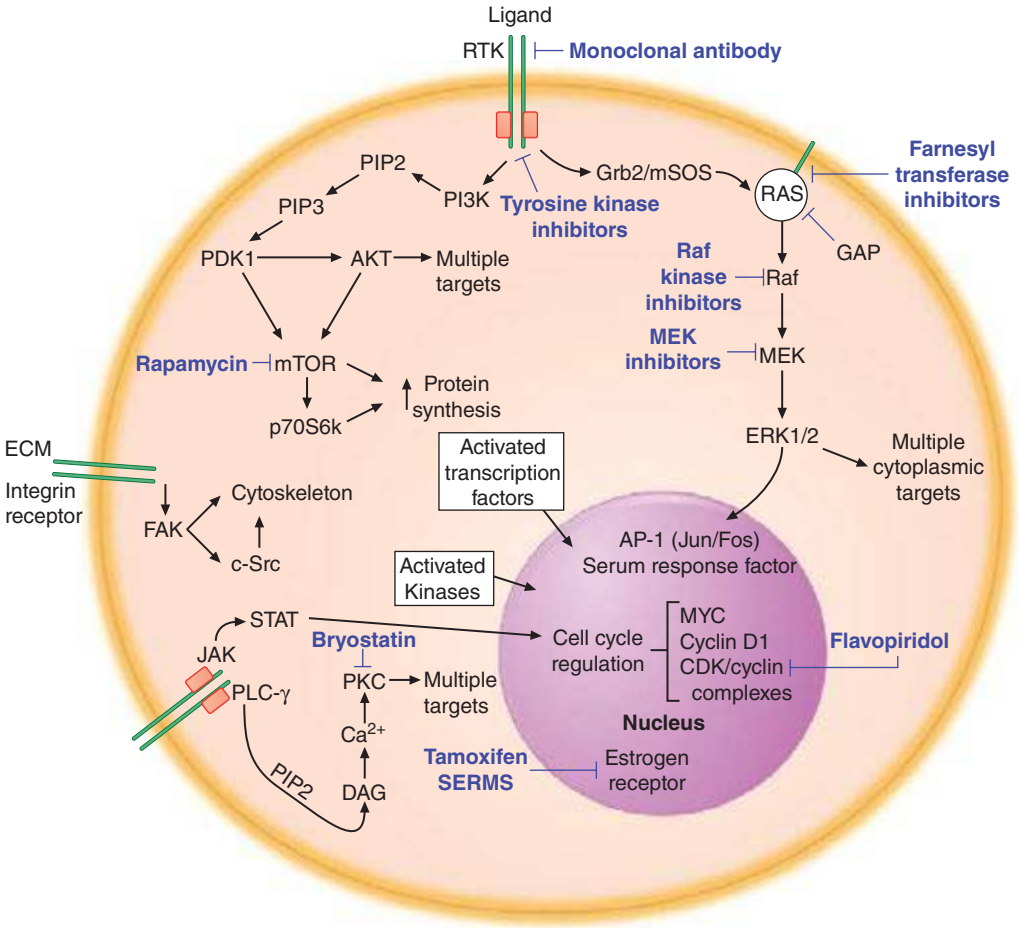

FIGURE 102e-2 **Therapeutic targeting of signal transduction pathways in cancer cells.** Three major signal transduction pathways are activated by receptor tyrosine kinases (RTK). ***1.*** The protooncogene Ras is activated by the Grb2/mSOS guanine nucleotide exchange factor, which induces an association with Raf and activation of downstream kinases (MEK and ERK1/2). ***2.*** Activated PI3K phosphorylates the membrane lipid PIP_2 to generate PIP_3, which acts as a membrane-docking site for a number of cellular proteins including the serine/threonine kinases PDK1 and Akt. PDK1 has numerous cellular targets, including Akt and mTOR. Akt phosphorylates target proteins that promote resistance to apoptosis and enhance cell cycle progression, whereas mTOR and its target p70S6K upregulate protein synthesis to potentiate cell growth. ***3.*** Activation of PLC-γ leads to the formation of diacylglycerol (DAG) and increased intracellular calcium, with activation of multiple isoforms of PKC and other enzymes regulated by the calcium/calmodulin system. Other important signaling pathways involve non-RTKs that are activated by cytokine or integrin receptors. Janus kinases (JAK) phosphorylate STAT (signal transducer and activator of transcription) transcription factors, which translocate to the nucleus and activate target genes. Integrin receptors mediate cellular interactions with the extracellular matrix (ECM), inducing activation of FAK (focal adhesion kinase) and c-Src, which activate multiple downstream pathways, including modulation of the cell cytoskeleton. Many activated kinases and transcription factors migrate into the nucleus, where they regulate gene transcription, thus completing the path from extracellular signals, such as growth factors, to a change in cell phenotype, such as induction of differentiation or cell proliferation. The nuclear targets of these processes include transcription factors (e.g., Myc, AP-1, and serum response factor) and the cell cycle machinery (CDKs and cyclins). Inhibitors of many of these pathways have been developed for the treatment of human cancers. Examples of inhibitors that are currently being evaluated in clinical trials are shown in purple type.

reactions. Mutation in the BCR-ABL kinase in the ATP-binding pocket (such as the threonine to isoleucine change at codon 315 [T315I]) can prevent imatinib binding. Other resistance mechanisms include altering other signal transduction pathways to bypass the inhibited pathway. As resistance mechanisms become better defined, rational strategies to overcome resistance will emerge. In addition, many kinase inhibitors are less specific for an oncogenic target than was hoped, and toxicities related to off-target inhibition of kinases limit the use of the agent at a dose that would optimally inhibit the cancer-relevant kinase.

Targeted agents can also be used to deliver highly toxic compounds. An important component of the technology for developing effective conjugates is the design of the linker between the two, which needs to be stable. Currently approved antibody drug conjugates include brentuximab vedotin, which links the microtubule toxin monomethyl auristatin E (MMAE) to an antibody targeting the cell surface antigen CD30, which is expressed on a number of malignant cells but especially in Hodgkin's disease and anaplastic lymphoma. The linker in this case is cleavable, which allows diffusion of the drug out of the cell after delivery. The second approved conjugate is ado-trastuzumab emtansine, which links the microtubule formation inhibitor mertansine and the monoclonal antibody trastuzumab targeted against human epidermal growth factor receptor 2 (HER2) on breast cancer cells. In this case, the linker is noncleavable, thus trapping the chemotherapeutic agent within the cells. There are theoretical pluses and minuses to having either cleavable or noncleavable linkers, and it is likely that both will be used in future developments of antibody-drug conjugates.

Another strategy to enhance the antitumor effects of targeted agents is to use them in rational combinations with each other and in empiric combinations with chemotherapy agents that kill cells in ways distinct from targeted agents. Combinations of trastuzumab (a monoclonal antibody that targets the HER2 receptor [member of the epidermal growth factor receptor (EGFR) family]) with chemotherapy have significant activity against breast and stomach cancers that have high levels of expression of the HER2 protein. The activity of trastuzumab