Protein phosphorylation catalyzed by protein kinases plays critical roles in the regulation of signal-transduction pathways. Deregulated kinase activity is observed in a variety of human diseases, such as cancer, making them targets for the development of molecular therapies. The PI3K/PTEN/AKT/mTOR and RAF/MEK/ERK signaling pathways play fundamental roles in transmitting signals from membrane receptors to downstream targets that regulate apoptosis, cell growth and angiogenesis. Accumulating evidence suggests that both pathways are constitutively activated through multiple genetic and epigenetic mechanisms in a wide variety of human malignancies and play several key functions in cancer development and progression; in that respect, both the PI3K and MAPK pathways function at the bottleneck of signal transduction through protein kinase cascades, thereby constituting attractive therapeutic targets for anti-cancer treatments. These pathways, however, are part of complicated and interwoven regulatory networks and recent evidence suggests that combining inhibitors targeting both the PI3K/PTEN/AKT/mTOR and the RAF/MEK/ERK pathways may avoid tumor escape from single-pathway blockade and ultimately suppress both malignant growth and survival more efficiently. Moreover, both pathways may converge on the regulation of crucial functions, such as neo-angiogenesis, involving not only the cancer cell but also the tumor stroma and the surrounding “normal” compartment. In this review, we describe recent advances in understanding the PI3K and MAPK pathways, in particular the mechanisms by which they regulate tumor growth and angiogenesis, and highlight the potential therapeutic opportunities for targeting these pathways for cancer treatment.