The PI3K/mTOR cascade plays an important role in controlling cell growth, proliferation and survival. Through various mechanisms, this pathway is frequently dysregulated in human cancers, suggesting the use of pathway modulators as novel targeted anticancer agents. To this end, substantial drug discovery efforts have been devoted both in pharmaceutical companies and in academia to identify and develop therapeutic agents able to specifically downregulate the kinase activity of mTOR and/or other components of the pathway. Compounds with different mechanisms of action (e.g., ATP and non-ATP competitive mTOR inhibitors) or protein kinase selectivity profiles (e.g., dual PI3K/mTOR versus selective mTOR inhibitors) have been exploited to inhibit the mTOR complexes, and some of these modulators have already provided proof-of-concept in cancer clinical settings. Thus, convincing clinical activity has been reported for the allosteric mTORC1 selective inhibitors in renal cell carcinoma, tuberousclerosis and lymphoma patients, and a few of these rapamycin derivatives have already received marketing approval. In an effort to expand the antitumor activity of the early allosteric inhibitors, ATP-competitive mTOR kinase inhibitors with different levels of selectivity against lipid and protein kinases have been identified and optimized, and some of these compounds are already in the early days of clinical evaluation. This oral communication will present and discuss the identification and early clinical evaluation of some of these PI3K/mTOR pathway modulators.