Breast cancer represents the most common malignancy among women in the developed world. Being a heterogeneous disease, it encompasses different molecular subtypes, with an abundance of molecular aberrations fueling its malignant growth. The identification of these aberrations leads to the clinical development of targeted therapeutics. In the setting of primary breast cancer this has been best exemplified by the development of trastuzumab, which changed the natural course of HER2-positive early-stage disease. Currently, the arena of targeted compounds assessed in primary breast cancer is largely pre-dominated by HER2 blocking agents, with pertuzumab, an anti-HER2 monoclonal antibody, trastuzumab-DM1, an antibody-drug conjugate and the anti-HER2 tyrosine kinase inhibitors afatinib and neratinib being the most developed ones. In particular the concept of dual HER2 blockade, based on the administration of non-cross-resistant HER2 blocking agents, has been successfully assessed in the neoadjuvant setting. In the adjuvant setting dual combinations of trastuzumab with either lapatinib or pertuzumab is under evaluation in large randomized phase III trials (ALTTO, APHINITY). Bevacizumab, an anti-VEGF compound representing the most extensively studied anti-angiogenic agent, is another targeted drug under development in primary breast cancer but initial results on its potential added value in early triple negative disease have been disappointing (BEATRICE trial). Another class of targeted compounds in clinical trials enrolling patients with early-stage breast cancer is the one of PI3K blocking agents. Everolimus, an mTOR inhibitor recently approved in hormone-refractory metastatic disease, is being assessed as adjuvant treatment in randomized phase III trials. Other PI3K blocking agents undergo clinical evaluation as parts of neoadjuvant regimens. Overall, targeted agents under development in primary breast cancer constitute an exciting field of oncology, giving hope for improved clinical outcomes.