Clinical research on cancer biomarkers is essential in understanding recent discoveries in cancer biology and heterogeneity of the cancer disease. However, there are only a few examples of clinically useful studies that have identified cancer biomarkers with clinical benefit. Urokinase-type plasminogen activator (uPA) and its inhibitor plasminogen activator inhibitor type 1 (PAI-1) are two of the few tumor tissue-associated cancer biomarkers that have been evaluated successfully and extensively in many preclinical and clinical studies for their clinical utility. Most of the studies have been conducted in early breast cancer to demonstrate the prognostic and predictive value for this malignancy. As a result of these investigations, uPA and PAI-1 have reached the highest level of clinical evidence, level of evidence 1. This article sheds light on the current status of major clinical Phase II and III breast cancer therapy trials (Chemo-N0, NNBC-3 and Plan B), and introduces ongoing clinical trials targeting uPA in advanced cancers of the breast and pancreas, employing synthetic small-size drugs to counteract uPA activity (WX-UK1, Mesupron®). The therapeutic effect of a uPA-derived small-size synthetic peptide (Å6) is tested in advanced ovarian cancer patients.