Susan G. Komen
Research Grants – Fiscal Year 2014

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Overcoming or preventing resistance to HER2 targeted therapies

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Lead Organization: Duke University School of Medicine
Grant Mechanism: KS **Grant ID:** SAC110033

Public Abstract:
Approximately 40,000 women die each year in the U.S. from breast cancer-related causes, with the overwhelming majority of those deaths due to progressive metastatic disease that has become resistant totherapy. Although there have been significant advancements in the treatment of inherently aggressive HER2+ breast cancers, the development of resistance to therapy has limited the clinical efficacy of HER2 targeted therapies, particularly in women with advanced stage breast cancer. Even those advanced stageHER2+ breast cancers that initially respond to T-DMl (trastuzumab-emtansine) will ultimately becomeresistant. If we cannot cure advanced stage breast cancer, we should strive to convert it to a manageable chronic disease similar to high blood pressure or diabetes. Development of resistance to HER2 targeted therapies does not appear to be caused by a single mechanism. Therefore, treatment strategies to overcome or prevent the onset of resistance to HER2 targeted therapies will require tailoring therapy based on a tumor profile predictive for the development of resistance via a specific mechanism(s). First however, we need to identify the different mechanisms involved in the development of therapeutic resistance. Here, we will investigate the role of a key regulator of tumor cell death, referred to as MDM2, in the development of resistance to HER2 targeted therapies, and other therapies used to treat non-HER2+ breast cancers. Our recent work showed that aberrant MDM2 activity in HER2+ breast cancer cells led to the development of resistance to the oral HER2 inhibitor lapatinib (Tykerb), which is currently approved for the treatment of HER2+ breast cancers. Importantly, in our laboratory studies, resistance to lapatinib could be overcome using an MDM2 inhibitor. Since MDM2 inhibitors are currently in clinical development, we expect that successful completion of our proposed research studies will lead to initiation of clinical trials evaluating the efficacy of an MDM2 inhibitor to overcome therapeutic resistance to HER2 targeted therapies mediated by persistent MDM2 activity. Enhancing the efficacy of HER2 targeted therapies by overcoming or ideally preventing the development of resistance will have a transformative impact by significantly prolonging survival in women with advanced and early stage HER2 targeted therapies. Our work to extend the relevance of MDM2 to resistance to therapies used to treat HER2 negative breast cancers, has the potential to broaden the impact on survival of breast cancer patients.