Susan G. Komen

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A role for PDK1 in acquired resistance to CDK4/6 inhibitors

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Public Abstract:

Breast cancer is the most common cancer diagnosed in American women and is the second leading cause of female cancer-related deaths. More than two-thirds of breast cancers express the estrogen receptor (ER) and thus depend on estrogen for growth. Treatment for ER-positive breast cancer is aimed at blocking ER function using antiestrogens such as tamoxifen, fulvestrant and aromatase inhibitors (letrozole, anastrozole). However, after an initial response to treatment many ER-positive tumors develop resistance and then progress, resulting in more women dying from ER-positive breast cancer than all other breast cancer types combined. Thus, it is absolutely critical to understand the mechanism of de novo and acquired resistance and to find better ways to target this major subtype of breast cancer in order to prevent deaths from this disease. One of the most promising new therapies for breast cancer is the development of cyclin-dependent kinase (CDK) 4/6 inhibitors. CDK4 and CDK6 are proteins involved in the regulation of the cell cycle pathway. Inhibition of CDK4 and CDK6 results in cell cycle arrest thus preventing the proliferation of cancer cells. Early clinical trials have shown that CDK4/6 inhibitors are active against ER-positive breast cancers and are likely to be approved for the treatment of patients with this cancer subtype. However, as for other targeted therapies, development of resistance to CDK4/6 inhibitors is expected. Our long-term goal is to identify novel therapeutic strategies capable of preventing and reversing clinical resistance to CDK4/6 inhibitors in ER-positive breast cancer. Based on preliminary data, we propose that 3-phosphoinositide dependent protein kinase 1 (PDK1) is important for the acquired resistance to CDK4/6 inhibitors, thus providing a rationale for therapeutic

targeting of PDK1 and CDK4/6 in combination as a novel treatment strategy for ER-positive breast cancer. In this proposal we will investigate the mechanisms by which PDK1 signaling is involved in the growth of breast cancer cells resistant to CDK4/6 inhibition. We will determine if the combination of PDK1 and CDK4/6 inhibition will result in superior antitumor activity in human ER-positive breast tumors that we will establish in experimental mice. In summary, this investigation should meaningfully contribute to the understanding of how ER-positive breast cancers acquire resistance to CDK4/6 inhibitors, and in turn contribute to the eradication of ER-positive breast cancer.