Abstract Title: - Unveiling the Breast Cancer Resistance Mechanism: Exploring Biomarkers Associated with CDK4/6 Inhibitor Resistance

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Aims: - Breast cancer is the most prevalent form of cancer in women across the world, especially among Indian women. The current treatment management of the disease involves a combination of surgery, radiotherapy, and chemotherapy. Alongside targeted and hormonal therapies are offered based on the presence of three markers - Estrogen receptor (ER), Progesterone receptor (PR), and Human epidermal growth factor receptor 2 (HER2). Cyclin-dependent kinase 4 and 6 (CDK4/6) inhibitors are the drugs that target CDK4 & CDK6 proteins and prevent cancer cell proliferation by arresting them at the G1-S checkpoint of the cell cycle. These inhibitors are used in combination with endocrine therapy and have significantly improved the progression-free survival (PFS) and overall survival (OS) of advanced and metastatic ER+HER2− breast cancer patients (MBC). There are three CDK4/6 inhibitors available: Palbociclib, Ribociclib, and Abemaciclib. It has been observed that CDK4/6 inhibitors can induce resistance in ER+HER2- MBC. Therefore, a reductionist approach is necessary to identify biomarkers for the molecular mechanisms responsible for drug resistance in breast cancer. This approach involves identifying key determinants such as tumor burden and growth kinetics, tumor heterogeneity, physical barriers, the immune system and the microenvironment, undruggable cancer drivers, and the consequences of applying therapeutic pressures.

Methods: - We plan to begin our work by using an in-silico approach to identify molecules. Additionally, we aim to find a marker signature that indicates resistance from liquid biopsy in the future. Identifying the molecular mechanisms responsible for this resistance will help in developing new therapeutic targets.

Results: - As part of our research, we are striving to uncover biomarkers that can predict the efficacy of CDK4/6 inhibitors even before their administration. In addition, we are working to identify biomarkers that can aid in reversing resistance to these inhibitors. By gaining a better understanding of the mechanisms of action of breast cancer treatments, we can not only enhance our comprehension of the mechanisms involved in the development of resistance, but we can also optimize existing treatment regimens.

Conclusions: - The prevalence of breast cancer necessitates a multifaceted treatment approach involving CDK4/6 inhibitors. However, the emergence of resistance calls for a reductionist approach to uncover molecular biomarkers. Our methods involve in-silico analysis and future liquid biopsy signature

identification. These efforts aim to predict treatment success and reverse resistance, ultimately advancing breast cancer treatment and understanding resistance mechanisms.