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Endocrine Therapy Mediated Breast Cancer Steven M Nguyen*

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Endocrine therapy is the first-line therapy for patients with hormone metastatic breast cancer. Although, resistance of endocrine frequently occurs during the course of the treatment. Cellular pathways involved in expansion are new drugs that combat the development of resistance. Cyclin-dependent kinases (CDKs) are a subgroup of serine/ threonine kinases that play a key role in regulating cell cycle progression. The currently approved and under investigation CDK inhibitors, also to the preclinical data is explained in this short communication. It is for the advantage of the treatment of HR+ breast cancer. As the efficiency and toxicity profile, with the exception of patients with advanced visceral disease, most patients will receive endocrine therapies (ET) in the treatment of HR+MBC. Unfortunately, not all patients respond to first-line ET due to intrinsic resistance, while others may initially respond but eventually progress with secondary acquired resistance leading to disease progression and endocrine resistance. Mechanisms of resistance to antiestrogen therapy include among others, estrogen receptor (ER) loss over time in the tumor which occurs in about 20% of patients treated with ET. Cell cycle regulation is identified as an attractive target for targeted drug therapy. Given their kinase activity, the cyclin dependent kinases have been pursued as drug targets. CDK 4/6 inhibitors prevent the cyclin D-CDK4/6 complex phosphorylation of Rb required for the commitment to S phase and ultimately, cellular mitosis. An additional suggested mechanism of action for the novel CDK 4/6 inhibitor, palbociclib, is decreasing the expression of cyclooxygenase-II (COX-II), an enzyme associated with the epithelial-mesenchymal transition (EMT) in metastasis. Preclinical data in melanoma cell lines, for example, have shown that pharmacological CDK 4/6 inhibition led to degradation of FOXM1 transcription factor and resulted in subsequent phenotypic expression of cellular senescence. Growth-promoting agents such as estrogen up-regulate cyclin D gene expression.

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Furthermore, CDK4/6 is particularly activated in ER+ breast cancer via the ER, along with other oncogenic signaling pathways. These pathways provide many alternative targets for agents that may be useful in combination with ET to decrease resistance to treatment and to extend benefit to patients who do not achieve optimal benefit from ET alone. However, it is unknown if there is benefit to the continuation of CDK 4/6 inhibitors following progression. Recent neoadjuvant studies have also demonstrated clinical activity when introducing these agents earlier. The future looks very promising for the ET of patients with MBC, with unprecedented PFS findings on recent trials; it is likely that the overall survival of patients will continue to improve overtime. Part of the success of these agents is in overcoming intrinsic resistance of cancer and preventing acquired resistance over time. However, the question remains on which patients are these drug combinations needed, as adding these agents to endocrine therapy increases toxicity.