Breast cancers that express the estrogen receptor and/or progesterone receptor are called hormone receptor positive breast cancer. The majority of breast cancers, including metastatic breast cancers, are hormone receptor positive. The estrogen receptor is a key driver of tumor development and progression, and endocrine therapies that target the estrogen receptor are the cornerstone treatment in hormone receptor positive breast cancer. More recently, the combination of endocrine therapy and CDK4/6 inhibitors, which target the cell cycle and cause cell cycle arrest, was shown to substantially improve progression free survival, and delay the need for chemotherapy regimens when compared to endocrine therapy alone. CDK4/6 inhibitors in combination with endocrine therapies are currently the standard first line treatment regimen after the diagnosis of metastatic hormone receptor positive breast cancer. This combination treatment is overall well tolerated, however, not all patients are sensitive and benefit from this regimen. Approximately 15% of patients have primary (intrinsic) resistance to the combination of endocrine therapy and CDK4/6 inhibitors and develop disease progression with a few months of treatment. On the other hand, there are patients that are highly sensitive and exhibit stable disease for many years while on this regimen.

Multiple pre-clinical and clinical studies have investigated mechanisms of resistance to CDK4/6 inhibitors and endocrine therapy. However, with the exception of the expression of the estrogen receptor, there are no biomarkers or other tools to determine upfront which patients with metastatic hormone receptor positive breast cancer are likely to benefit from CDK4/6 inhibitors and endocrine therapy, and which patients will be resistant. This is of utmost importance, since patients with intrinsic resistance to this combination should receive a different treatment that is more effective. Having a tool to determine benefit from this regimen would enable clinicians to personalize treatment regimens and offer a regimen that would potentially yield better long-term outcomes. Currently there are other effective targeted treatments approved for metastatic hormone receptor positive breast cancer that target other pathways as well as recently approved antibody drug conjugates. Therefore, for patients that have intrinsic resistance to CDK4/6 inhibitors and endocrine therapy there are other first line treatment options. In addition, a tool that can identify patients that are resistant to CDK4/6 inhibitors and endocrine therapy will facilitate clinical trials and enable better selection of patients for trials evaluating novel agents for metastatic disease, including agents that are added to CDK4/6 inhibitors and endocrine therapy that can overcome resistance to this treatment combination. On the other hand, this tool will enable the exclusion of patients that are likely to have prolonged disease control with a CDK4/6 inhibitor and endocrine treatment only and spare these patients from investigational agents that may have more side effects.

Currently, there are tools to select treatment regimens for early-stage primary hormone receptor breast cancer, such as the OncotypeDX test. Although OncotypeDX test is a robust tool that was validated in retrospective and more recently in prospective studies, OncotypeDX and similar tools are mostly based on gene expression profiling and can be time consuming, expensive, and not accessible to all patients worldwide. Therefore, ideally, a tool that can help to personalize and optimize treatments for metastatic hormone receptor positive breast cancer should have rapid results and be accessible to all patients.

To address these gaps, we propose to develop a tool that will stratify metastatic tumors that are sensitive to CDK4/6 inhibitors and endocrine therapy versus resistant. To develop this tool, we will use machine learning algorithms that will incorporate: (i) clinical information such as age, time to disease recurrence from the diagnosis of early-stage disease (ii) standard pathology information such as tumor grade, estrogen receptor, progesterone and (iii) detailed single cell analysis of the tumor immune microenvironment. The tool itself will require the use of standard pathology images of the tumor, tumor markers that are routinely assessed for clinical purposes (estrogen receptor, progesterone receptor and HER2 expression) and clinical data to predict treatment benefit.

Beyond the development of the tool that ultimately can be applied in clinical practice, through the proposed study we will gain insights into the mechanisms of resistance to CDK4/6 inhibitors and endocrine therapy. Particularly, mechanisms of resistance to CDK4/6 inhibitors and endocrine therapy that pertain to the tumor immune microenvironment have not been extensively studied yet. Herein, we plan to perform a comprehensive analysis of the tumor immune microenvironment at the single cell level. This information will set the stage for future pre-clinical and clinical studies of novel immune therapies for the treatment of metastatic hormone receptor positive breast cancer.