Estrogen receptor (ER) positive breast cancer, comprising of about 70% of breast tumors, is the most common sub-type of breast cancer. While there are multiple endocrine therapies available, such as tamoxifen, aromatase inhibitors (e.g., anastrozole, letrozole and exemestane), fulvestrant, about 30% of patients with metastatic breast cancer who have tumor progression on one endocrine therapy do not respond to additional endocrine therapy. In some patients the disease progression is due to incomplete suppression of the ER pathway, while in others it is due to ER-independent signaling from alternate growth factors pathways. Our group, along with others, recently demonstrated the presence of acquired mutations in the ligand binding domain of estrogen receptor (ESR1) which can lead to constitutional activation of the estrogen receptor in the absence of ligand (estrogen), and thereby result in resistance to standard endocrine therapies particularly aromatase inhibitors [1–4]. In the talk, we will briefly review the mechanisms of resistance to endocrine therapy in breast cancer including role of ESR1 mutations, and the role of novel estrogen receptor degraders as well as rational combination of endocrine therapy with targeted therapies to treat patients with metastatic breast cancer.

**references**