Approximately 70% of all metastatic breast cancers (MBCs) express estrogen receptor (ER). Hormonal therapies targeting ER are highly active against these cancers and have been remarkably successful in improving outcomes. Unfortunately, resistance to hormonal therapy is nearly universal, and over 90% of patients develop resistance to various drugs targeting ER. We have identified mutations in three non-overlapping gene sets that are associated with the hormone-resistant phenotype: (1) ER α1, (2) MAPK pathway, and (3) transcription factors. (Figure 1). The finding of mutations that might activate MAPK signaling was particularly striking given the known oncogenic function of this pathway in other cancers and the potential to target this pathway with selective inhibitors.

Indeed, in preclinical models, the combination of an allosteric MEK inhibitor with an ER antagonist induced tumor regression in NF1-null, ERα-expressing xenografts that were resistant to anti-estrogen monotherapy. These data suggest that MAPK pathway alterations promote resistance to ER-targeted therapies in MBC and lead us to hypothesize that MAPK-targeted therapies will prove highly effective in such patients. However, NF1 (p = 0.001) is only one of several RAS modulators that are associated with hormone resistance, and we also see KRAS and HRAS mutations in this dataset. Further, RTK alterations (EGFR amplification and ERBB2 somatic mutations) and mutations in the RAF/MEK kinase cascade (BRAF and MEK1) are present and may comparably confer hormone resistance and sensitivity to MAPK pathway inhibition. We hypothesize that MAPK pathway-activated MBCs can be effectively treated using MAPK-targeted therapies in combination with hormonal therapy.

Rationale

We hypothesize that MAPK pathway-activated MBCs can be effectively treated using MAPK-targeted therapies in combination with hormonal therapy; however, the optimal way to inhibit the MAPK pathway in these tumors is unknown. We will perform a phase Ib/II clinical trial of the allosteric MEK1/2 inhibitor mirdametinib with the ER antagonist fulvestrant.

Mirdametinib Background

- Mirdametinib (PD-0325901) is a potent, selective MEK1/2 inhibitor
- IC50 = 15 nM on MEK enzyme
- Clinical antitumor activity has been shown at doses of 2mg/kg 3 times daily (up to 4mg) BID
- Mirdametinib (PD-0325901) is a potent, selective
- Half life of ~16h at 2mg BID
- Generally well tolerated at doses thought to be clinically active

Patient Accrual

The workflow to enroll patients to clinical trials at MSKCC is automated such that genomic alterations that are deposited on the cBioPortal are matched with appropriate clinical trials using database queries. A recent query of cBioPortal data from ER+ MBC patients treated at MSKCC showed 216 patients harboring actionable alterations in the MAPK pathway.

Future Directions

1. Responders will be stratified based on their enrolling MAPK alteration, and cell-free DNA (cfDNA) samples will be utilized to track response to treatment.
2. Explore how clinical and genomic variables precondition response to treatment.
3. Utilize biopsy specimens from enrolled patients to investigate biomarkers associated with response to treatment and to further develop models of MAPK-activated ER+ breast cancer.