A Phase 1b / 2a, Open-label Platform Study to Evaluate Mirdametinib in Combination with Fulvestrant in ER+ Metastatic Breast Cancers Harboring MAPK-activating Mutations

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Introduction

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) ESR1, (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, ER+ 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 (prevalence 6%) 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.

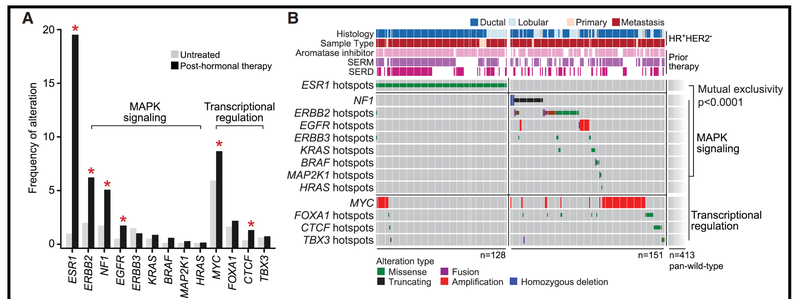

Figure 1. MAPK pathway alterations in ER+ MBC. A. Enrichment of alterations in genes in primary and metastatic cancers showing enrichment of ESR1, NF1 and ERBB2 alterations following AI therapy in ER+ MBC. B. Genomic alterations in ESR1-mutant vs. WT tumors showing MAPK pathway alterations clustered within ESR1-WT tumors. (Razavi et al, Cancer Cell 2018).

Genomic heterogeneity across these MBC patients. Within the MSK-IMPACT dataset, we have identified 1,680 patients with ER+ MBC, of which 216 harbor oncogenic alterations in components of the MAPK pathway (Figure 2). No specific alteration in the MAPK pathway predominates. Among these 216, 37 (17%) have ESR1 mutations, but only 22 of these overlap with the MAPK genes above, showing under-enrichment (p = 0.003), indicating that this is therefore a distinct and non-overlapping mechanism of resistance.

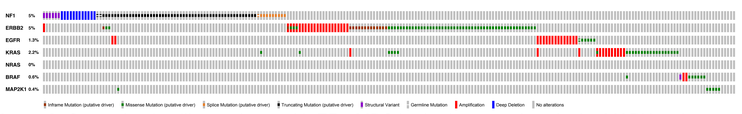

Figure 2. Oncoprint detailing patients with ER+ MBC harboring mutations in the MAPK pathway or in ESR1, treated at MSK.

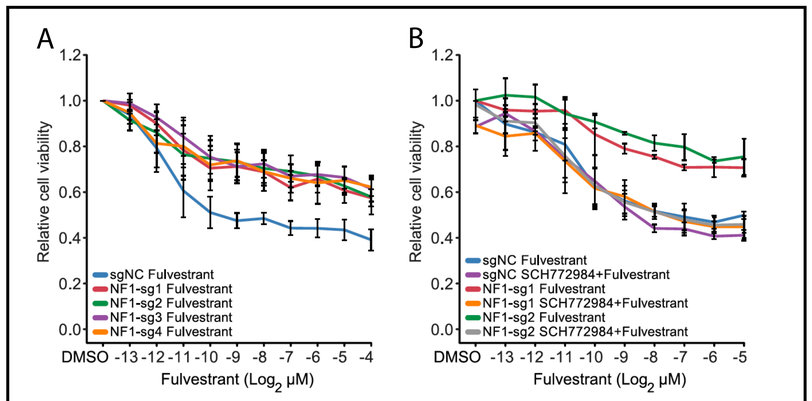

Figure 3. Functional validation of MAPK activation as a mechanism of resistance to endocrine therapy. A, B. Proliferation curves for MCF7 cells in which NF1 was knocked down using CRISPR or transfected with empty vector, treated with fulvestrant (left) or fulvestrant + ERK inhibitor (SCH772984) (right). (Razavi et al, Cancer Cell 2018).

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/IIa 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/m^2 (up to 4mg) BID
- Half life of ~16h at 2mg BID
- MTD is 15mg BID continuous
- Generally well tolerated at doses thought to be clinically active
- Currently being developed both as monotherapy and in combination therapies

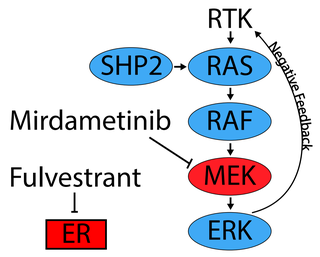

Figure 4. Schematic showing the way in which the MAPK pathway can be inhibited using the MEK inibitor mirdametinib.

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.

Trial Design

Eligibility

Metastatic ER+ BC s/p CDK4/6i → Fulvestrant Mirdametinib (MEKi)

Key Inclusion Criteria:
- ER+ tumor (ASCO-CAP guidelines) harboring MAPK pathway alteration
- Unlimited Number of Prior Therapies Allowed
- Measurable Disease Necessary
- Required Progression on At Least One Line of Endocrine Therapy

Primary Endpoints:
Safety and Tolerability
Best objective response by RECIST 1.1

Secondary Endpoints:
Clinical Benefit Rate (RECIST 1.1)
Progression Free Survival and Duration of Response

The feasibility of the combination will be established in a brief safety run-in of full dose fulvestrant together with mirdametinib with dose de-escalation planned if two Dose Limiting Toxicities (DLT) are observed in the first 6 patients utilizing 3+3 design.

This drug combination will then be expanded in three cohorts of patients defined by tumor genotype:
(1) RAS activating - NF1 loss, KRAS or HRAS activating mutation
(2) RTK – EGFR amplification or ERBB2 hotspot mutation
(3) RAF/MEK – activating mutation in BRAF, CRAF, or MEK1/2

This trial is currently open to accrual at Memorial Sloan Kettering and is registered as NCT05054374.

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.