Therapeutic Implications of Concurrent ESR1 and PI3K Pathway Mutations in HR+/HER2- Metastatic Breast Cancer

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Background

- Individualized cancer treatments have revolutionized oncologic care
- Next generation sequencing (NGS) can identify mutations that impact prognosis, disease recurrence, and treatment for breast cancer patients
- Mutations in the ESR1 gene confer resistance to endocrine therapies by enabling estrogen receptor (ER) activity independent of estrogen binding
- PIK3CA mutations activate the PI3k/AKT/mTOR signaling pathway promoting cellular proliferation, signaling, and metabolism
- The EMERALD trial demonstrated that elacestrant significantly prolonged PFS in patients with advanced hormone positive breast cancer and ESR1 mutations
- SOLAR-1 and CAPItello-291 showed alpelisib and capivasertib improved PFS in patients with PIK3CA-mutated, HR-positive, HER2-negative advanced breast cancer who had progressed on prior endocrine therapy, respectively
- Little is known about the management of patients with concurrent mutations

Objectives

- Identify patients at Henry Ford with concurrent ESR1 and PI3k pathway mutations who received elacestrant and a PI3k inhibitor (alpelisib or capivasertib)
- Estimate progression free survival (PFS) and overall survival (OS) for patients receiving sequential ESR1i → PIK3CAi versus PIK3CAi → ESR1i
- Compare outcomes between the two sequencing strategies and evaluate the impact of treatment chronology on breast cancer patients

Methods

- Performed a retrospective chart review of patients who received both ESR1i and PI3ki and reviewed Tempus data for breast oncologists at Henry Ford. The goal was to identify patients with concurrent ESR1 and PI3k pathway mutations who received both ESR1i and PI3ki.
- Collected variables included source of NGS testing, age, date of diagnosis, date of mutation detection, treatment start and stop dates, reason for treatment discontinuation, prior therapies, and sites of metastatic disease
- PFS was calculated from the date the first treatment was initiated to the date of first progression or last follow-up; OS was calculated from the date of first treatment to the date of death or last follow-up
- Median PFS, OS, and 95% CI were reported. When median OS was not reached, 1-year and 18-months survival probability were reported

Results

- Patients with concurrent mutations who were treated with alpelistib had a median PFS of 8.08 mo (95% CI: 0.00-25.83) and median OS of 17.12 mo (95% CI: 6.93-27.31)
- Capivasertib had median PFS of 4.67 mo (95% CI: 0.70-8.64) and all patients remained alive at time of data collection
- Median PFS for elacestrant was 8.08 mo (95% CI: 3.66-12.51) and median OS was not reached (NR). 1 year survival probability was 100% and 18 months was 58.3%
- Patients who received both elacestrant and a PIK3CA inhibitor had median PFS of 5.62 mo (95% CI: 4.40-6.84), median OS of 49.81 mo (95% CI: NR- NR)
- When patients received elacestrant first, followed by a PIK3CA inhibitor, median PFS was 4.67 mo (95% CI: 2.70-6.65), 1 year survival probability was 100% and 2 year was 75%
- If a PIK3CA inhibitor was given first followed by elacestrant, median PFS was 8.08 mo (95% CI: 1.77-14.39), median OS was 50.79 (95% CI:NR-NR)
- Patients with only bone metastases had a PFS of 14.69 mo (95% CI: 0.00-32.86), OS of 50.79 mo (95% CI: NR-NR)
- Those with visceral metastases had PFS of 5.62 mo (95% CI: 3.86-7.38), OS was not reached. 1-year prob was 100% and 18 months was 66.7%

ESR1i First

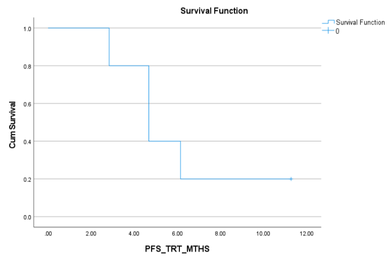


Figure 1: Median PFS when patients with concurrent ESR1 and PI3k pathway mutations were given elacestrant first followed by PI3ki

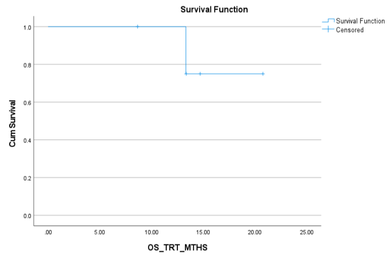


Figure 2: Median OS when patients with concurrent ESR1 and PI3k pathway mutations were given elacestrant first followed by PI3ki

PI3ki First

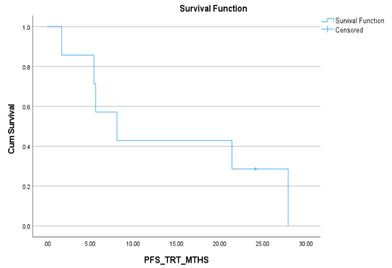


Figure 3: Median PFS when patients with concurrent ESR1 and PI3k pathway mutations were given PI3ki (capivasertib or alpelisib) first followed by ESR1i

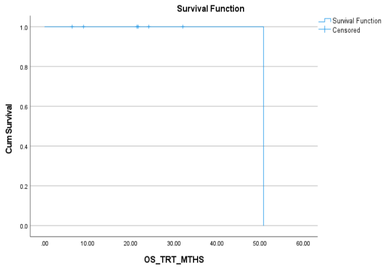


Figure 4: Median OS when patients with concurrent ESR1 and PI3k pathway mutations were given PI3ki (capivasertib or alpelisib) first followed by ESR1i

Conclusions

- Our data uniquely demonstrates outcomes of patients with concurrent ESR1 and PIK3CA mutations
- Treatment sequencing that consisted of PIK3CAi → ESR1i resulted in longer PFS and OS
- This sequencing may offer improved outcomes, as PI3k mutations may confer a worse prognosis than ESR1 mutations. This was seen in prior studies (EMERALD and EMBER-3) when patients treated with oral SERDs and PI3k mutations had shorter PFS compared to patients without PI3k pathway alterations.

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