ESR1 mutations, ESR1 fusions and co-occurring alterations assessed in breast cancer tumors

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Abstract

Background: ESR1 mutations and fusions arise in hormone receptor positive (HR+)/PR+ breast cancer patients after aromatase inhibitor (AI) therapy (low estrogen states), to become constitutively active in a ligand independent manner. Patients with tumors harboring ESR1 D538G/P537S mutations (by digital droplet PCR of ctDNA) exhibit worse prognosis and reduced survival rate in determining benefit of chemotherapy vs tamoxifen treatment after progression on AI (Augusto, et al. ASCO 2016). A retrospective analysis of the ESR1 mutation frequency and co-occurring alterations that could guide subsequent therapy approaches was investigated.

Methods: Molecular profiles of 416 breast tumors (HR+/PR+) breast cancer patients (52-76%) were assessed. Proteon expression (IHC) and gene amplification (ISH) were performed. Genomic testing included stool-genome capture NGS (NextSeq Illumina platforms) and ArcherES fusion assay based on anchored multiplex PCR (AMP) FusionPlexSolid Tool. ESR1 variant (ESR1variant/fusion)/mutation profiles and HR+/BC patients lacking gene alterations (ESR1 WT) were compared; Pearson’s chi- squared test was used to test for significant differences.

Results: An ESR1 mutation (point mutations, insertion deletions 3477 and fusions) [n=139] was detected in 13% (50/384) of the specimens, and this constitutes 21% (91/427) of all HR+/breast cancers. Two NGS patterns were detected ESR1 variants (D538G mutation in exon 7 and A495S in exon 9, both are classified as variants of unknown significance). ESR1 mutations were not detected in HER2– BC. Seventy-seven percent of patients with ESR1 mutations were detected in metastatic specimens (p=0.03), with liver (29/33 or 86%) and bone (9/8 or 15%) as the most frequent sources for ESR1 variant (ESR1var) positivity. The most common alleles detected were: D538G [24%], Y537S [16%], V546S [15%] and L536H [15%]; 15 other additional alleles were detected (each 2%). ESR1 fusions were detected in 4 ESR1 WT patients: ESR1–ATF2B, ESR1–MUK1, ESR1–TRNK8C, ESR1–ARN2 and ESR1–CDM9PF1. We next compared ESR1 variant (mutation/fusion) profiles to HR+ breast patients lacking gene alterations (ESR1 WT) (EFS). EFS was present in 100% and 96% of ESR1 var and ESR1 WT BC, respectively, however expression of PR was negative in 23% and 30% of ESR1var and WT BC, respectively (p=0.05). Significantly higher rates of other gene amplification events observed in ESR1 WT BC: (a) ESR1 WT included: ESR1–ATF2B, ESR1–MUK1, ESR1–TRNK8C, ESR1–ARN2 and ESR1–CDM9PF1. We next compared ESR1 variant (mutation/fusion) profiles to HR+ breast patients lacking gene alterations (ESR1 WT) (EFS). EFS was present in 100% and 96% of ESR1 var and ESR1 WT BC, respectively, however expression of PR was negative in 23% and 30% of ESR1var and WT BC, respectively (p=0.05). Significantly higher rates of other gene amplification events observed in ESR1 WT BC: (a) ESR1 WT included: ESR1–ATF2B, ESR1–MUK1, ESR1–TRNK8C, ESR1–ARN2 and ESR1–CDM9PF1. In interactional transrepression (20% vs. 7%), CD53 (51% vs. 28%), CCND2 (50% vs. 0%), FGFR (37% vs. 36%), APO3 (40% vs. 18%) and FGFR1(24% vs. 15%), whereas MYC was more frequently amplified in ESR1 WT BC (17% vs. 2%); all p-values <0.05. KRAS mutations were higher in ESR1 WT BC (30% vs. 0%); ONF. Alterations in the PI3K/AKT/mTOR pathway were common in both ESR1 var and ESR1 WT BC: ESR1 var patients, PI3KCA, AKT and PTEN were observed in 82% and 27%; 4% and 8% and 5% respectively, and PTEN loss by IHC in 29% and 25%. Conclusions: ESR1 mutations and fusions are detected in 25% of HR–BC, the majority of which are in metastatic sites. Amplifications of genes involved in downstream regulatory pathways were present and may contribute to the poor prognosis of ESR1var BC. Correlation with antecdent therapy is currently underway.

Conclusions

• ESR1 variants were detected in 21% of hormone receptor positive breast cancer patients receiving fulvestrant. PR expression was more varied. Three of the four patients with ESR1 fusions lacked PR expression.
• Co-occurring alterations with ESR1 mutations may lend support to novel combinatorial treatment strategies.