PS2-08-17: Prevalence and clinical significance of exon 6 *ESR1* gene fusions in advanced breast cancer after disease progression on aromatase inhibitor therapy

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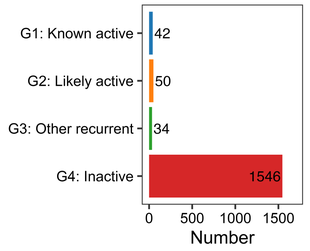
Background

Endocrine therapy resistance (ETR) is a frequent challenge in metastatic ER+ HER2- breast cancer (mBC) and is driven by different molecular mechanisms. Since the first observation of a transcriptionally active *ESR1* fusion involving exons 1-6 (e6) of *ESR1* fused to YAP1,[1] exon 6 *ESR1* gene fusions are increasingly recognized as a cause of ETR. However, subsequent studies have found that 3' fusion partners are highly heterogeneous, leading to questions regarding clinical actionability and effects on outcomes. Here, we report an *ESR1* fusion classification system with real world evidence (RWE) to support clinical utility.

Methods

- *ESR1* fusions were detected in circulating tumor DNA (ctDNA) by sequencing the intronic region between exons 6 and 7 to identify fusion breakpoints from the GuardantINFORM™ RWE database. A total of 1,676 *ESR1* fusions were detected and classified into four groups based on Gou *et al.*:[2]
  - **G1 (known active):** Lab-tested active partners.
  - **G2 (likely active):** Not lab-tested but partner is a transcription factor (TF) or transcriptional co-activator (CoA) and observed ≥2 times.
  - **G3 (other recurrent):** Not TF/CoA but recurrent in ≥3 cases.
  - **G4 (inactive):** All other fusions (eg, *ESR1* fusions not involving exon 6, out-of-frame, chromosome 6 partner in-frame, exon-to-exon, or *ESR1*-to-*ESR1*).
- Patients were grouped as Active Fusion (G1–G3), or Inactive (G4).
- The index date was defined as the start of the first endocrine-containing regimen following or during detection of *ESR1* fusion status This date served as time zero for overall survival (OS) analyses and Kaplan-Meier curves.
- OS for patients receiving endocrine-only regimens was analyzed using a multivariable Cox proportional hazards model adjusting for fusion status (active or inactive), age, number of prior treatment lines, and methylated DNA–based tumor fraction.

Active *ESR1* fusion partners (G1-G3) detected in ctDNA



G1 partners: *YAP1* (24), *ARNT2* (11), *GRIP1* (2), *LPP* (2), *PCDH11X* (2), *TNRC6B* (1).

G2 partners: *SMAD4* (6), *CRTC3* (4), *ESSRG* (5), *HNF4G* (4), *NFAT5* (4), *SS18* (4), *WWTR1* (4), *KDM2A* (3), *NCOA6* (3), *CTNND2* (2), *EP300* (2), *IRF3* (2), *NCOA2* (2), *NFIB* (2), *PAX2* (2).

G3 partners: *PXN1* (10), *TFG* (8), *PROSER1* (4), *ATRNL1* (3), *GAB1* (3), *HGS* (3), *SIPA1L1* (3).

Figure 1: Active *ESR1* exon 6 containing fusion partners identified by sequencing ctDNA.

Active *ESR1* fusions are associated with poor survival with endocrine monotherapy but not in combination with CDK4/6i

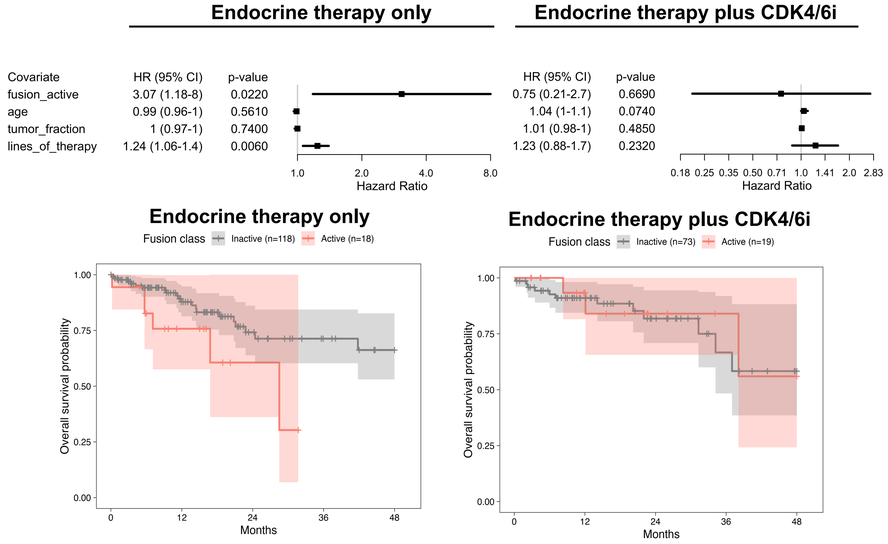


Figure 2: Multivariate analysis showing patients with active (G1-3) *ESR1* fusions receiving endocrine only second-line treatment had significantly worse survival when compared the inactive fusion group (G4).

ESR1 fusions and mutations significantly co-occur

		***ESR1* hotspot mutation**	
		Yes	**No**
***ESR1* fusion present** (Known active, likely active, other recurrent)	**Yes**	42	29
	No	3,172	13,472

Figure 3: Co-occurrence of *ESR1* fusions and activating mutations in ctDNA from breast cancer patients, with Fisher's exact test showing strong association (odds ratio = 6.15, P = 1.20×10^{-13}).

Conclusions

- Despite low prevalence, estimated at 2.1%, in ER+ HER2- mBC cases post aromatase inhibitor therapy, G1-3 *ESR1* fusions were associated with an increased risk of early death when managed with second-line endocrine monotherapy regimens but not if a CDK4/6i combination was used (consistent with preclinical modelling and aligns with evidence of CDK4/6i activity in tumors harboring ESR1 fusions).[2,3]
- *ESR1* fusions co-occur with *ESR1* hotspot activating mutations indicating relevance of these findings to oral SERD treatment.
- These results suggest that endocrine monotherapy should be avoided in patients with G1-3 *ESR1* fusions.

References

1. Li S, *et al.* Endocrine-therapy-resistant ESR1 variants revealed by genomic characterization of breast-cancer-derived xenografts. *Cell Rep*. 2013. PMID: 24055055.
2. Gou X, *et al.* Kinome Reprogramming Is a Targetable Vulnerability in ESR1 Fusion-Driven Breast Cancer. *Cancer Res.* 2023. PMID: 37071495.
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Acknowledgments

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