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Elevated Expression of STK3 mRNA and Protein is Associated with Poor Outcome in Invasive Breast Cancer

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Purpose of the study: The mammalian sterile 20-like kinase (MST2/STK3) and its close homologue MST1(STK4) are members of the germinal centre kinase group II (GCK II) family of mitogen-activated protein kinases (MAPK). High STK3 expression is known to be correlated with poor prognosis in various cancers playing a role in cell migration and invasion. This study aimed to determine correlations of STK3 expression with clinicopathological variables in BCs.

Methods: STK3 mRNA expression was investigated in the METABRIC BC cohort (n=1980) and externally validated using online BC expression datasets [bc-GenExMiner v4.0]. STK3 protein expression was studied in a well characterised series of primary invasive BCs (n=1024) using immunohistochemistry including correlations with clinicopathological parameters, other biomarkers and patient outcome.

Results: Copy number (CN) gain of STK3 was correlated with adverse prognostic features: higher grade and poor NPI ($p<0.0001$) High STK3 expression was also associated with poor prognostic factors, including high grade, younger age, larger tumour size, poorer NPI and negative ER/PR status ($p<0.001$). In PAM50 subtypes, high STK3 expression was associated with Luminal B/basal like tumours. Cytoplasmic STK3 (c-STK3) protein expression was associated with increased mitotic index, poorer NPI

(p<0.001) and basal-like markers CK5/6 and EGFR (p<0.05). In univariate analysis, high c-STK3 expression showed poorer outcome in the whole cohort and ER+ subgroups (p<0.05). Pooled STK3 gene expression data in the external validation cohort confirmed association with poor outcome (p<0.0001, HR = 1.60, 95% CI 1.28–2.01).

Conclusions: Results suggest c-STK3 as a poor prognostic marker in invasive BC including ER+ subgroups warranting further functional studies.

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