Genomic landscape of HER2-negative advanced or metastatic breast cancer with *PIK3CA* gain-of-function mutations

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INTRODUCTION

Alpelisib and fulvestrant are used as a combination treatment option for postmenopausal *PIK3CA*-mutated, hormone receptor positive (HR+), human epidermal growth factor receptor 2-negative (HER2−), advanced or metastatic breast cancer (a/mBC) patients. However, despite the presence of activating mutations in *PIK3CA*, many patients do not derive benefit, or ultimately progress while on alpelisib therapy. In the current study, we investigate the genomic landscape of *PIK3CA*-mutated, HER2− a/mBC using next-generation sequencing (NGS) to provide insight into possible mechanisms of therapeutic resistance to alpelisib/fulvestrant and to identify potential targetable pathways.

METHODS

We utilized the Tempus integrated data platform to retrospectively analyze de-identified NGS data from 2,918 a/mBC patients with formalin-fixed, paraffin-embedded tumor biopsies sequenced using the the Tempus xO, xE but primarily the xT solid tumor assay (DNA-seq of 595-648 genes at 500x coverage, full-transcriptome RNA-seq). The mutations identified for this study include somatic single-nucleotide variants, insertions/ deletions and copy number variations (gains defined as ≥8 copies). Curated clinical data was utilized to determine HER2 and hormone receptor (ER/PR) status.

COLLABORATIVE INSTITUTIONS

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RESULTS

PIK3CA mutational landscape in HER2− a/mBC

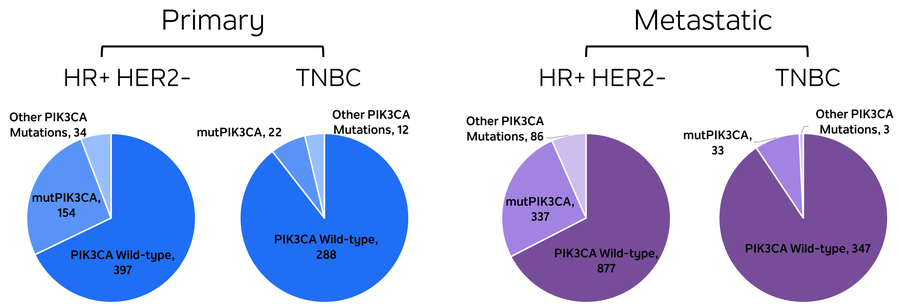

Figure 1. We analyzed a total of 2,918 a/mBC tumors and identified a subset of 907 primary and 1,618 metastatic tumors that were negative for HER2 (HER2-) expression based on curated immunohistochemistry staining.

Next-generation DNA sequencing identified molecular alterations in *PIK3CA* in 222 primary and 459 metastatic HER2- tumors, which were further categorized as mut*PIK3CA* if among the 11 common *PIK3CA* alterations associated with the alpelisib companion diagnostic test (H1047R, E545K, E542K, C420R, E545A, E545D, E545G, Q546E, Q546R, H1047L, or H1047Y), or other *PIK3CA* mutations if they fell outside of this category.

mut*PIK3CA* was detected in 154 (26.3%) and 22 (6.8%) of hormone receptor positive (HR+) HER2- or triple negative (TNBC) primary tumors respectively, compared to 337 (25.9%) or 33 (8.6%) hormone receptor positive (HR+) HER2- or triple negative (TNBC) metastatic tumors, respectively.

Genomic features of mut*PIK3CA*, HER2− a/mBC

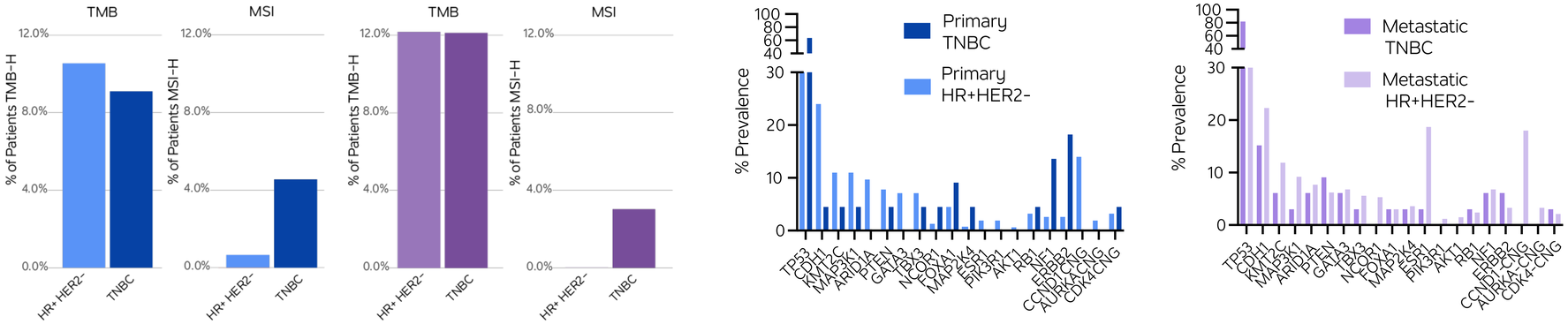

Figure 2. Our investigation focused on mut*PIK3CA* HER2- a/mBCs to identify additional molecular features of interest.

(A) Tumor mutational burden high (TMB-H; defined as ≥10 mutations/MB) was detected in 10.4% and 9.1% of mut*PIK3CA* HR+ and TNBC tumors, respectively. Among the mut*PIK3CA* HER2- metastatic tumors, TMB-H was detected in 12.2% and 12.1% of HR+ and TNBC tumors, respectively. Microsatellite instability high (MSI-H) was detected in 0.6% or 4.5% of primary HR+ HER2- or TNBC mut*PIK3CA* tumors respectively, compared to 3% of metastatic TNBC mut*PIK3CA* tumors (MSI-H not detected in metastatic HR+ HER2- mut*PIK3CA* tumors).

(B) The most commonly co-mutated genes among primary or metastatic mut*PIK3CA* HER2− samples were *TP53*, *CDH1*, *ESR1*, *KMT2C*, *MAP3K1*, *ARID1A*, *PTEN*, *GATA3*, *NF1*, and *TBX3* among others ; some genes have been implicated in resistance to endocrine therapy or PI3K inhibitors. In HR+ disease, when primary is compared to metastatic, metastatic tumors had an apparent higher frequency of mutations in genes implicated in endocrine resistance, such as *ESR1* (18.7% vs 1.9%), *ERBB2* (3.3% vs 2.6%), *NF1* (6.8% vs 2.6%), compared to primary tumors, although statistical analysis was not performed. Additionally, copy number gains (CNG) were identified in several cell cycle genes, including: *CCND1*, *CDK4*, and *AURKA* across these tumor types.

CONCLUSIONS

- There is substantial genomic heterogeneity among mut*PIK3CA*, HER2− a/mBCs.
- Through comparisons between primary and metastatic samples and HR+ and TNBC subtypes, co-mutations that occur alongside mut*PIK3CA* were identified and could potentially be exploited by targeted therapies. Future studies are needed to assess the prognostic/predictive role of these and other candidate gene alterations.
- Further analyses at the transcript-level are the subject of on-going research.