Biomarkers associated with resistance or response to CDK4/6 treatment in patients with metastatic hormone-receptive positive breast cancer

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INTRODUCTION

CDK4/6 inhibitor (CDKI) drugs are the current standard of care for treatment of first and second-line hormone-receptor positive/HER2 negative (HR+/HER2-) metastatic breast cancers. To date, no biomarker of response has been identified. Treatment-induced RB1 mutations were noted as mechanism of resistance to palbociclib and fulvestrant in about 5% of patients treated on PALOMA3 trials, whereas PI3K and ESR1 mutations emerged as potential resistance to the anti-hormonal backbone1. Additionally, FGFR1 amplification has been suggested as a resistance pathway to fulvestrant and ribociclib2. Utilizing next-gen sequencing (NGS), chromogenic in situ hybridization (CISH) and immunohistochemistry (IHC) (Caris Life Sciences, Phoenix, AZ) data from n=155 attempted to retrospectively identify a molecular signature of resistance or response as retrospectively measured by PFS.

METHODS

Specimens were profiled using massively parallel NGS sequencing using either a 45-gene TruSeq Amplicon panel (n=) or a 592-gene SureSelect XT panel (Agilent, Santa Clara, CA). Sequencing was performed on an Illumina MiSeq or NextSeq instrument for the 45- and 592-gene panels respectively (Illumina, San Diego, CA). Only alterations with known pathogenic potential were considered aberrant. Copy number alterations (CNA) were also explored on samples profiled with the 592-gene NGS panel. Gains ≥6 copies were considered amplified.

All IHC stains were performed using automated platforms (Benchmark, Ventana Medical Systems and Dako Autostainer, Agilent) at CLIA/CAP/ISO15189/NYSDOH certified clinical laboratory (Caris Life Sciences, Phoenix, AZ). PD-L1 expression was evaluated in the tumor cells (TC) using SP142 (Ventana).

DATA ANALYSIS

BIOMARKER ANALYSIS

Table 2. PFS Calculated for Mutated Biomarkers

**References available upon request.**

**CONCLUSIONS**

- NSD3 gene amplification appears to be the only alteration that may significantly affect tumor CDK4/6 response. NSD3 gene is a member of DNA methyltransferase pathway and highly correlated with ESR1 and ERs.
- Three biomarkers, RB1, CDH1, TML3+77 mutations are significantly more frequent in post-palbociclib biopsies.
- FGFR1 does not appear to play a clinical role in our population.
- RB1 mutations are present post-treatment, but are infrequent.
- ESR1, PI3K, ARID1A are numerically more frequently seen in post treatment biopsies.
- TP53 mutation represents poor prognosis regardless of line of therapy or treatment option.
- This study is limited by its retrospective nature and relatively small numbers. Further testing will be required to confirm the relationships observed.