Actionable co-alterations in breast tumors with pathogenic mutations in the homologous recombination DNA damage repair pathway


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INTRODUCTION AND PURPOSE

- Homologous recombination deficiency (HRD) is common in breast cancer, with somatic frequencies of 15.6% previously reported.
- Targeted therapies including PARP inhibitors may provide effective and tolerable therapies for patients with breast cancer harboring germline or somatic HRD.
- We evaluated the relationship between HRD and the presence of additional mutations that may impact responsiveness to targeted therapies beyond PARP inhibitors in patients with breast cancer.

METHODS

- Comprehensive molecular profiling of 4,647 breast tumors was performed at Caris Life Sciences, Inc using 592 gene Next Generation Sequencing (NGS), average depth 500X.
- Complete molecular profiles were retrospectively reviewed to identify pathogenic or presumed pathogenic somatic mutations in the homologous recombination DNA damage repair (HR-DDR) genes ARID1A, ATM, ATXN, BAP1, BARD1, BLM, BRCAl/2, BRRP1, CHEK1/2, FANCA/C/D2/E/F/G/L, KMT2D, MRE11, NBN, RAD50/S1/S1B, PALB2 & WRN, as well as 39 markers that may be associated with treatment response to targeted anti-cancer therapies.
- Frequencies of co-alterations (mutation-overexpression) of interest were calculated and compared between breast tumors that had a pathogenic or presumed pathogenic somatic mutation in a gene involved in the HR-DDR pathway (HR-MT) and breast tumors with an intact HR-DDR pathway (HR-WT)- and by breast cancer subtype (hormone receptor [hr] positive, HER2 positive, and triple negative).

RESULTS

- HRD was identified in 17.9% of the 4,647 evaluable breast cancers, with somatic frequencies of 15.6% previously reported.
- Distribution of HR gene mutations in all breast tumors and by subtype
- TMB in HR-MT breast tumors vs HR-WT breast tumors
- Markers of response to therapy

CONCLUSIONS

- In breast cancer, HR-MT is common and is associated with markers of response to immunotherapy.
- Co-alterations (mutation/overexpression) were identified in both HR-MT and HR-WT tumors that suggest other targets for treatment.
- 94.9% of the co-alterations predict responsiveness to currently available treatments.

INFORMATION

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