

Conference Abstracts

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Genomic landscape of TP53 Y220C–mutated clinically advanced prostate carcinoma (CAPC)

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Abstract

Background

The TP53 Y220C base substitution mutation has become a significant therapeutic target with the development of reactivator drugs that restore TP53 function with a regulatory function in the cell cycle. However, its real-world prevalence and associated genomic landscape is not established in CAPC. Data on concurrent genomic alterations (GA) may guide the development of combinatorial therapeutic strategies.

Methods

26,156 cases of CAPC underwent hybrid capture-based comprehensive genomic profiling (CGP) to study all classes of GA including base substitutions, short insertions, deletions, copy

number changes, rearrangements and fusions. Microsatellite instability (MSI) status and tumor mutation burden (TMB) were determined from the sequencing data; comparisons utilized the Fisher Exact method.

Results

144 CAPC (0.6%) of CAPC cases featured TP53 Y220C mutation (TP53 Y220C+). Patients with TP53 Y220C+ CAPC had slightly higher mean age (70.0 vs 68.2; $p = 0.020$). GA potentially associated with CAPC primary hormonal-based therapy response more frequently found in TP53 Y220C+ cases included SPOP (10.5% vs 1.4%; $p < 0.0001$). GA linked to PARP inhibitor response slightly more frequent in TP53 Y220C+ cases included BRCA2 GA (8.7% vs 3.5%; $p = 0.0003$) and ATM GA (5.9% vs 4.2%; NS). GA in RAD21

were slightly higher in TP53 Y220C- CAPC (14.8% vs 8.3%; $p = 0.029$). Additional selected GA, MSI status, and TMB are presented in the table below.

Conclusion

TP53 Y220C is a rare finding in CAPC, but it may offer a potential therapeutic avenue for these patients whose tumors feature such a mutation. In

addition, TP53 Y220C+ cases appear to be genomically relatively distinct from TP53 Y220C- CAPC cases and may feature genomic signatures that could influence treatment selection and trial design. Study limitations include a retrospective, descriptive design, a lack of clinical data annotation, and selection and confounding biases, so our findings are hypothesis-generating.

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