Clinical Outcomes in CDK12 Mutant Advanced Prostate Cancer

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Background: CDK12 loss occurs in 3-7% of metastatic prostate cancer and is characterized by a genomic instability signature, but the clinical implications of CDK12 loss are not well established.

Methods: To determine the clinical course of patients with CDK12 mutant advanced prostate cancer compared with other genomic subtypes, we conducted a retrospective chart review from three academic medical centers. 317 patients with advanced prostate cancer and prior next-generation sequencing (NGS) from tumor tissue (n = 172) or circulating tumor DNA (n = 145). Patients were stratified by mutation status (CDK12, homologous recombination deficiencies (HRD: BRCA1/2 and ATM), TP53 and Other cohort). 46 patients had CDK12 mutations; 34 had biallelic CDK12 loss (79%). Kaplan-Meier method was used to evaluate time to event outcomes: time to development of metastatic disease, time to development of castration-resistance, and time to PSA progression after first-line androgen receptor inhibitor therapy (ARPI) in a patient subset.

Results and Limitations: Median follow-up was 66.6 months. Patients with CDK12 mutant prostate cancer exhibited shorter time to metastasis (median = 34.9 months, p-value = 0.004) and development of castration-resistant disease (median = 32.7 months, p-value < 0.001), compared to other genomic subtypes, with shorter time to PSA progression on first-line ARPI treatment of metastatic castration resistant disease (median = 3.6 months, p-value = 0.0219). CDK12 mutant patients did not have an overall shorter time on treatment compared with other mutation subgroups, and CDK12 status did not demonstrate statistical significance in multivariate analysis. Limitations include variable center-dependent practice patterns and heterogeneity due to combining tumor and liquid biopsy data.

Conclusions: Our data suggest that advanced prostate cancers harboring CDK12 mutations display aggressive clinical behavior, underscoring the need to fully delineate the molecular and clinical characteristics, and appropriate therapeutic approaches for distinct subtypes of advanced prostate cancers.

Conflicts of Interest: None related to this study

Funding Acknowledgements: This work was supported by funds from the Prostate Cancer Foundation and the National Cancer Institute (R01CA230516). AMC is an Investigator with the Howards Hughes Medical Institute.