Clinical Outcomes in CDK12 Mutant Advanced Prostate Cancer

Melissa A. Reimers[a]*, Steven M. Yip[b]*, **Jonathan Chou [c,d]***, Li Zhang[c,d,e], Marcin Cieslik[g,h], Mallika Dhawan[c,d], Bruce Montgomery[k,l], Alexander W. Wyatt[m], Kim N. Chi[b,m], Eric J. Small[c,d], Arul M. Chinnaiyan[g,h,i,j], Ajjai S. Alva[a,g**], and Felix Y. Feng[c,d,f**]

[a] Department of Internal Medicine, Division of Hematology/Oncology, University of Michigan
[b] BC CANCER, 600 W 10th Ave, Vancouver, BC
[c] Department of Medicine, Division of Hematology/Oncology, University of California San Francisco
[d]Helen Diller Family Comprehensive Cancer Center, University of California San Francisco
[e] Department of Epidemiology and Biostatistics, University of California San Francisco
[f] Departments of Radiation Oncology and Urology, University of California San Francisco
[g] Michigan Center for Translational Pathology, University of Michigan, Ann Arbor, MI, USA
[h] Department of Pathology, University of Michigan, Ann Arbor, MI, USA
[i] Department of Urology, University of Michigan, Ann Arbor, MI, USA
[j] Howard Hughes Medical Institute, University of Michigan, Ann Arbor, MI, USA
[k] Department of Medicine, University of Washington, Seattle, WA, USA
[l] Veterans Affairs Puget Sound Health Care System, University of Washington, Seattle, WA, USA
[m] Vancouver Prostate Centre, Department of Urologic Sciences, University of British Columbia
*These authors contributed equally
**Co-corresponding authors

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.