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Pan-cancer Analysis of *CDK12* Alterations Identifies a Subset of Prostate Cancers with Distinct Genomic and Clinical Characteristics

Bastien Nguyen[a,b,c], **Jose Mauricio Mota**[d], **Subhiksha Nandakumar**[a,b,c], **Konrad H. Stopsack**[e], **Emily Weg**[f], **Dana Rathkopf**[d], **Michael J. Morris**[d], **Howard I. Scher**[d], **Philip W. Kantoff**[e], **Anuradha Gopalan**[g], **Dmitriy Zamarin**[h], **David B. Solit**[a,b,d], **Nikolaus Schultz**[a,b,c], **Wassim Abida**[d,*]

[a]Marie-Josée and Henry R. Kravis Center for Molecular Oncology, Memorial Sloan Kettering Cancer Center, New York, NY, USA

[b]Human Oncology and Pathogenesis Program, Memorial Sloan Kettering Cancer Center, New York, NY, USA

[c]Department of Epidemiology & Biostatistics, Memorial Sloan Kettering Cancer Center, New York, NY, USA

[d]Genitourinary Oncology Service, Department of Medicine, Memorial Sloan Kettering Cancer Center, New York, NY, USA

[e]Department of Medicine, Memorial Sloan Kettering Cancer Center, New York, NY, USA

[f]Department of Radiation Oncology, Memorial Sloan Kettering Cancer Center, New York, NY, USA

[g]Department of Pathology, Memorial Sloan Kettering Cancer Center, New York, NY, USA

[*]Corresponding author. Genitourinary Oncology Service, Department of Medicine, Memorial Sloan Kettering Cancer Center, 1275 York Avenue, New York, NY 10065, USA. Tel. +1 646 4224633. abidam@mskcc.org (W. Abida).

Author contributions: Wassim Abida had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Study concept and design: Nguyen, Mota, Nandakumar, Gopalan, Schultz, Abida.

Acquisition of data: Nguyen, Mota, Nandakumar, Stopsack, Weg, Rathkopf, Morris, Scher, Zamarin, Abida.

Analysis and interpretation of data: Nguyen, Mota, Nandakumar, Stopsack, Kantoff, Gopalan, Zamarin, Solit, Schultz, Abida.

Drafting of the manuscript: Nguyen, Mota, Stopsack, Schultz, Abida. Critical revision of the manuscript for important intellectual content: All authors.

Statistical analysis: Nguyen, Stopsack, Schultz.

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Supervision: Schultz, Abida.

Other: None.

CRediT authorship contribution statement

Bastien Nguyen: Data curation, Formal analysis, Investigation, Methodology, Visualization, Writing - original draft, Writing - review & editing. **Jose Mauricio Mota:** Data curation, Formal analysis, Investigation, Methodology, Writing - original draft, Writing - review & editing. **Subhiksha Nandakumar:** Data curation, Formal analysis, Investigation, Methodology, Visualization, Writing - review & editing. **Konrad H. Stopsack:** Methodology, Validation, Writing - review & editing. **Emily Weg:** Writing - review & editing. **Dana Rathkopf:** Writing - review & editing. **Michael J. Morris:** Writing - review & editing. **Howard I. Scher:** Funding acquisition, Writing - review & editing. **Philip W. Kantoff:** Funding acquisition, Writing - review & editing. **Anuradha Gopalan:** Formal analysis, Investigation, Writing - review & editing. **Dmitriy Zamarin:** Investigation, Validation, Writing - review & editing. **David B. Solit:** Supervision, Writing - review & editing. **Nikolaus Schultz:** Conceptualization, Funding acquisition, Supervision, Writing - original draft, Writing - review & editing. **Wassim Abida:** Conceptualization, Funding acquisition, Supervision, Writing - original draft, Writing - review & editing.

Appendix A. Supplementary data

Supplementary material related to this article can be found, in the online version, at doi:https://doi.org/10.1016/j.eururo.2020.03.024.

[h]Gynecologic Medical Oncology Service, Department of Medicine, Memorial Sloan Kettering Cancer Center, New York, NY, USA

Abstract

Background—*CDK12* genomic alterations occur in several tumor types, but little is known about their oncogenic role and clinical significance.

Objective—To describe the landscape of *CDK12* alterations across solid cancers and the clinical features of *CDK12*-altered prostate cancer.

Design, setting, and participants—A single-center retrospective study of 26743 patients across 25 solid tumor types who underwent tumor sequencing was performed. Clinicopathologic features and outcomes were assessed in prostate cancer.

Outcome measurements and statistical analysis—*CDK12* alterations and their association with genomic characteristics are described. For prostate cancer patients, overall survival and time to castration resistance were assessed using univariable and multivariable Cox regression analysis.

Results and limitations—*CDK12* alterations were identified in 404/26743 patients (1.5%) overall, but were most frequent in prostate (100/1875, 5.3%) and ovarian cancer (43/1034, 4.2%), in which they were associated with a high prevalence of truncating variants and biallelic inactivation. *CDK12* alterations defined a genomic subtype of prostate cancer with a unique copy-number alteration profile and involvement of distinct oncogenic pathway alterations, including cell-cycle pathway genes. *CDK12*-altered prostate cancer was associated with somewhat more aggressive clinical features and shorter overall survival (median 64.4 vs 74.9 mo; $p = 0.032$) independent of standard clinical factors and tumor copy-number alteration burden (adjusted hazard ratio 1.80, 95% confidence interval 1.12–2.89; $p = 0.024$). The study is limited by its retrospective nature.

Conclusions—*CDK12* alteration is a rare event across solid cancers but defines a clinically distinct molecular subtype of prostate cancer associated with unique genomic alterations and slightly more aggressive clinical features.

Patient summary—*CDK12* gene alterations occur rarely across tumor types, but more frequently in prostate cancer, where they are associated with genomic instability, cell-cycle pathway gene alterations, and somewhat worse clinical outcomes, warranting further investigation of therapeutic targeting of this disease subset.

Keywords

CDK12; Clinical sequencing; Genomics; Prostate cancer; Tumor biology

1. Introduction

Genomic alterations in *CDK12* have been observed in various cancer types [1–4] but their oncogenic function and clinical relevance are poorly understood. *CDK12* encodes a cyclin-dependent serine/threonine kinase involved in the regulation of the cell cycle and of DNA repair by homologous recombination (HR). Specifically, it has been shown that *CDK12* loss

of function suppresses the expression of several HR genes, at least in part, via intronic polyadenylation [5–8]. Growing evidence suggests that biallelic *CDK12* loss determines a distinct phenotype of ovarian and prostate cancer characterized by high genomic instability and tandem duplications [9–11].

It has been reported that *CDK12* alterations occur in 4–11 % of prostate cancer cases and are more frequent in the metastatic castration-resistant setting (mCRPC) [3,9,12]. Despite preclinical work suggesting that *CDK12* loss or inhibition could impair genes in the HR repair pathway, recent evidence has shown that PARP inhibitors have limited efficacy in mCRPC patients harboring a *CDK12* alteration [13,14]. However, Wu and colleagues [9] recently demonstrated that *CDK12* loss determines a novel molecular subtype of prostate cancer associated with a higher proportion of fusion neoantigens and potentially high immune infiltration and response to anti–PD1/PD-L1 agents.

In this study we sought to survey the landscape of *CDK12* mutations across different cancer types. We identified prostate cancer as the cancer type with the highest prevalence of *CDK12* oncogenic alterations and the largest proportion of truncating variants, with biallelic inactivation occurring frequently, and characterized the genomic architecture of *CDK12*-altered prostate carcinomas. We describe clinicopathologic characteristics and clinical outcomes for patients with prostate cancers harboring *CDK12* alterations. Our work adds to recent publications [15,16] by integrating pan-cancer genomic analysis from a clinical sequencing assay, identifying distinct genomic alterations associated with *CDK12*-altered prostate cancer, and describing clinical features of the largest set of prostate cancer patients with *CDK12* alterations identified using a single assay.

2. Patients and methods

2.1. Study design and patients

All patients in the study underwent tumor sequencing performed using the Memorial Sloan Kettering Integrated Molecular Profiling of Actionable Cancer Targets (MSK-IMPACT) clinical sequencing assay, a hybridization capture-based, next-generation sequencing platform, with 341, 410, or 468 genes (all panels included *CDK12)* [17,18]. After excluding 1965 cases with high microsatellite instability (MSI) cases, defined as an MSI sensor [19] score >10, and/or high tumor mutation burden (TMB) cases, defined as TMB ≥ 20 mutations/Mb, because of the high likelihood of passenger alterations in *CDK12,* a total of 26743 patients across 25 solid tumor types (minimum number of patients 100 per cancer type) who had MSK-IMPACT sequencing between July 2014 and April 12, 2019 were assessed for the presence of *CDK12* alterations. For patients with multiple sequenced samples, one sample was selected according to the following hierarchy: tumor purity (highest tumor purity as assessed by pathologist), gene panels (most recent), and coverage (highest sample sequencing coverage). Chart review was performed to extract clinical and pathologic data for prostate cancer patients. Data collection and retrospective analysis were performed with approval from the MSKCC institutional review board.

2.2. Genomic analysis

TMB was calculated as the total number of nonsynonymous mutations excluding *CDK12,* divided by the number of bases sequenced. Recurrent oncogenic alterations were defined as oncogenic according to OncoKB [20] (version August 28, 2019) and present in at least 1% in the whole cohort. Canonical oncogenic pathway-level alterations were computed using curated pathway templates [21]. MutSigCV v.1.4 was used to determine significantly mutated genes (false discovery rate [FDR] <0.1) [22]. Segmented copy-number data were processed using the CNtools package v1.4. The fraction of genome altered (FGA) was calculated for each sample as the percentage of the genome with log2 copy ratios >0.2 or < −0.2. Thresholds for copy-number alteration gain and loss were set at log2 copy ratios of >0.2 and <−0.2, respectively. *CDK12* biallelic (*CDK12*-Bi) inactivation was defined as either deep deletion, two or more deleterious mutations in the same tumor sample, one mutation with concurrent heterozygous loss of the wild-type (WT) allele, or one mutation with concurrent copy-neutral loss-of-heterozygosity (CN-LOH) as computed using the FACETS algorithm [23]. FACETS is an allele-specific copy-number analysis pipeline providing accurate, purity- and ploidy-corrected, integer DNA copy-number calls and cancer cell fraction (CCF) from sequencing data. Integer copy-number calls were used to determine the presence of *CDK12*-Bi inactivation due to heterozygous loss of the WT allele or CN-LOH. FACETS was also used to determine clonality. Mutations were defined as clonal if the upper bound of the 95% confidence interval (CI) for CCF was ≥0.8, and all other mutations were called subclonal. Of note, samples with *CDK12* rearrangement events were excluded in the biallelic analysis.

2.3. Prostate cancer outcomes

Baseline clinical characteristics and outcomes were available for a subset of patients with histologically confirmed prostate cancer who underwent tumor genomic profiling. Outcomes assessed were overall survival (OS), time to castration resistance, and time on treatment with first-line abiraterone acetate or enzalutamide for castration-resistant disease (Supplementary Fig. 1). For OS, follow-up started at the time of first metastasis and ended with patient death, with censorship occurring at last patient contact. For time to castration-resistance, follow-up started at the time of start of continuous androgen deprivation therapy (ADT) and ended at the development of castration-resistant disease as documented in the medical record, with censorship occurring at last patient assessment. For time-on-treatment analysis, follow-up started at the time of starting the agent as first-line therapy for CRPC and ended with discontinuation of the agent, with censorship occurring at last patient assessment. Median follow-up time was calculated for patients without the event only.

2.4. Statistical analysis

The Kruskal-Wallis test was used to evaluate differences in TMB, FGA, number of breakpoints, median segment size, tumor purity, and sequencing coverage among the three groups defined by *CDK12* allelic status (*CDK12*-WT vs *CDK12* monoallelic [*CDK12*-Mono] vs *CDK12-Bi).* We used a pairwise post-hoc Mann-Whitney test corrected for multiple comparisons using the FDR method. Fisher's exact test (adjusted for multiple comparisons) was used to evaluate differences in the prevalence of copy-number gain and

copy-number loss, and the prevalence of oncogenic pathway alterations based on *CDK12* allelic status. We used a binomial test to determine whether the ratio of missense mutations present in the kinase domain of *CDK12* differed significantly from the proportion of nucleic acids present in the kinase domain of *CDK12.* We used the Wilcoxon signed-rank test to determine whether TMB, FGA, and the number of breakpoints differed significantly between paired samples collected at two different time points. Time-to-event outcomes were analyzed using the Kaplan-Meier method and compared via the log-rank test. The association between *CDK12* alteration and survival was evaluated using univariable and multivariable Cox proportional-hazards regression models. Multivariable analysis was adjusted for standard clinical prognostic factors: age at diagnosis (continuous), Gleason score at diagnosis (<8 vs ≥8), prostate-specific antigen (PSA) at diagnosis (continuous), visceral metastasis at diagnosis (presence vs absence), de novo metastatic status at diagnosis (presence vs absence), and FGA. Multivariable tests were performed using analysis of variance to compare the models with and without the extra term. The p values reported are two-tailed. When applicable, multiple testing correction was performed using the FDR method and FDR < 0.05 was considered significant. All analyses were performed using R v3.5.2 (www.R-project.org) and Bioconductor v3.4.

3. Results

3.1. *Landscape of* CDK12 *alterations across cancer types*

We assessed the prevalence of *CDK12* alterations among 26743 patients across 25 solid cancer types profiled using the MSK-IMPACT clinical sequencing test. A total of 404 patients (1.5%) had tumors with at least one *CDK12* alteration. Prostate (n = 100/1875, 5.3%) and ovarian (n = 43/1034, 4.2%) cancers were the types with the highest frequencies of *CDK12* oncogenic alterations (Fig. 1A), including somatic point mutations, rearrangements, and deep deletions. Using MutSigCV [22], we found that *CDK12* was significantly recurrently mutated only in prostate and ovarian cancers compared with background mutation rates (FDR < 0.001 and FDR = 0.056, respectively; Fig. 1A). The majority of *CDK12* alterations in prostate cancer were truncating mutations, followed by missense mutations, rearrangements, and deep deletions (Supplementary Fig. 2A,B). Most truncating mutations were located within or upstream of the kinase domain (101/105, 96%), whereas missense mutations were more frequently clustered within the kinase domain (25/30, 83%), which was higher than expected by chance (p < 0.001; Fig. 1B), suggesting that these mutations probably have a deleterious effect on *CDK12* function. Moreover, in prostate cancer the majority of patients with missense mutations in the kinase domain of *CDK12* (18/24, 75%) had a concurrent truncating mutation suggestive of *CDK12*-Bi inactivation, which was not observed in other cancer types. In total, we identified 61/84 (73%) and 26/28 patients (93%) with putative *CDK12*-Bi inactivation in prostate and ovarian cancer, respectively (Fig. 1C). The principal genomic event responsible for *CDK12*-Bi inactivation in prostate cancer was multiple concurrent mutations of *CDK12* (49/61, 75%), whereas in ovarian cancer it was LOH (20/26, 77%; Fig. 1C). We observed a higher prevalence of clonal *CDK12* mutations than non-*CDK12* mutations in prostate and ovarian cancer (105/116 [91%] vs 140/196 [71%]; p < 0.001; and 26/30 [87%] vs 82/130 [63%]; p = 0.016, respectively; Fig. 1D, Supplementary Fig. 2C).

Of 14 prostate cancer patients with more than one tumor sequenced longitudinally, 13 showed shared *CDK12* alterations among all matched tumors, with one patient having samples collected up to 7.8 yr apart (Fig. 1E). Of note, the only patient who did not have shared *CDK12* alterations in their matched tumors had a *CDK12* rearrangement known to be prone to false-negative results in hybrid capture DNA sequencing. FGA and the number of breakpoints increased over time, whereas TMB did not change significantly between paired samples (Supplementary Fig. 2D). The frequency of *CDK12*-Bi inactivation did not differ between primary (34/48, 70%) and metastatic tumors (27/36, 75%) in which zygosity could be determined. These analyses suggest that *CDK12* alteration is an early event in the genomic makeup of *CDK12*-altered metastatic prostate cancer.

3.2. *Genomic architecture of* CDK12*-altered prostate cancer*

Of 84/100 *CDK12*-altered prostate cancers for which zygosity could be determined, 23 had CDK12 monoallelic inactivation (CDK12-Mono) and 61 had biallelic inactivation (CDK12-Bi). There was no difference in tumor purity or sequencing coverage by *CDK12* alteration status (Supplementary Fig. 3A,B). TMB and overall FGA were similar between *CDK12* -WT, *CDK12*-Mono, and *CDK12-Bi* (Fig. 2A, B), but we observed a higher fraction of genome gain in *CDK12*-Bi prostate cancer (Supplementary Fig. 3C). Of note, *CDK12*-Bi prostate cancer was associated with a higher number of breakpoints and smaller median size of copy-number–altered segments (Fig. 2C,D and Supplementary Fig. 3E,F). We compared copy-number alteration patterns and found that 13% of the evaluated genome was differentially affected between *CDK12*-WT and *CDK12*-Bi cases (Fig. 2E and Supplementary Table 1). This highly fragmented genome with a pattern of narrow spikes in copy-number–altered segments distributed along the genome (Fig. 2E) is suggestive of a tandem duplicator phenotype [9]. Chromosome 11q13.3, a locus that includes *CCND1, FGF19, FGF4,* and *FGF3,* was more frequently affected by copy-number gain in *CDK12*-Bi than in *CDK12*-WT tumors. Overall, these results suggest that *CDK12*-Bi inactivation may shape the genomic architecture of prostate cancer.

3.3. *Oncogenic alterations associated with* CDK12*-altered prostate cancer*

We investigated differences in the prevalence of 53 recurrent oncogenic alterations (Methods 2.2and Supplementary Table 2) by *CDK12* allelic status. We found eight recurrent oncogenic alterations that differed in prevalence by *CDK12* status (FDR < 0.05; Fig. 3A and Supplementary Table 2): *CCND1, MCL1,* and *MYC* were more frequently amplified, *FANCA* was more frequently lost, and *FOXA1* was more frequently mutated in the *CDK12*-Bi group. *TP53* mutations and *TMPRSS2-ERG* fusions were less frequently observed in the *CDK12*-Bi group. Next, we interrogated the alteration prevalence of ten canonical oncogenic signaling pathways: cell cycle, Hippo, Myc, Notch, Nrf2, PI-3-Kinase/Akt, RTK-RAS, TGFβ signaling, p53, and β-catenin/Wnt [21]. The cell cycle pathway was more frequently altered in *CDK12*-Bi than in *CDK12*-WT tumors, whereas alterations in the p53, PI-3–Kinase/Akt, and β-catenin/Wnt pathways were less frequently observed in *CDK12*-Bi than in *CDK12*-WT tumors (Fig. 3B).

3.4. *Clinicopathologic features and outcomes for* CDK12*-altered prostate cancer*

A subset of 1465 patients with prostate cancer were evaluable for clinical outcomes, of whom 100 had *CDK12* alterations and 1365 were *CDK12*-WT (Supplementary Fig. 1). Baseline clinicopathologic characteristics are shown in Table 1. Patients with *CDK12*-altered tumors had clinical features associated with worse prognosis, including a higher prevalence of de novo metastatic disease (40% vs 26%), higher PSA at diagnosis (median 14.8 vs 9.0 ng/mL), and a higher prevalence of Gleason score ≥8 (80% vs 57%). Patients with *CDK12*-Bi inactivation had the worst baseline characteristics (Supplementary Table 4). Clinical status at the time of tissue collection for molecular profiling is summarized in Supplementary Table S4 and shown in cBioPortal [26] (www.cbioportal.org/study?id=prad_cdk12_mskcc_2020). We interrogated the association between *CDK12* status and OS. There were a total of 315 deaths (*CDK12*-WT: 290/874 evaluable patients; *CDK12*-altered: 25/71) and the median follow-up time for censored patients was 30.2 mo. Compared to *CDK12*-WT patients, patients in the *CDK12*-altered group had shorter OS from diagnosis of metastatic disease (median 64.4 vs 74.9 mo; Fig. 4A). This difference was maintained after adjustment for known prognostic factors, including FGA [24] (adjusted hazard ratio [aHR] 1.80, 95% CI 1.12–2.89; $p = 0.024$). We also examined time to castration resistance from the start of ADT. There were a total of 522 events (*CDK12*-WT: 468/662 evaluable patients; *CDK12*-altered: 54/61) and the median follow-up time for censored patients was 12.2 mo. Patients in the *CDK12*-altered group had a shorter time to the development of castration-resistant disease (median 10.8 vs 13.1 mo; aHR 1.49, 95% CI 1.09–2.03; $p = 0.017$; Fig. 4B). Finally, among patients who received first-line abiraterone or enzalutamide for castration-resistant disease, those with *CDK12*-altered tumors had a similar time on treatment compared to *CDK12*-WT patients (median 9.7 vs 8.7 mo; aHR 1.08, 95% CI 0.57–1.51; $p = 0.8$; Supplementary Fig. 4). Collectively, these results suggest that *CDK12* oncogenic alterations define a subset of somewhat more aggressive prostate cancer that progresses slightly more rapidly to castration resistance and is associated with slightly worse survival.

4. Discussion

We analyzed the prevalence and types of somatic *CDK12* alterations across >26000 tumors spanning 25 cancer types and found that prostate and ovarian cancers were the malignancies with the highest prevalence of *CDK12* alterations, similar to a recent report [15]. The overall prevalence of *CDK12* alterations in prostate cancer was 5.3%, which falls within the previously reported range [3,15]. The majority of *CDK12* alterations in these cancers were oncogenic and clonal and resulted in biallelic inactivation, suggesting that *CDK12* loss of function has an important biological role in a subset of prostate and ovarian cancers. In prostate cancer in particular, the main event presumed to be responsible for *CDK12*-Bi inactivation is the co-occurrence of two deleterious mutations, whereas in *CDK12*-altered ovarian cancer it is an LOH event, which can span a larger chromosomal segment and may not be specific to *CDK12.* While we were not able to definitively demonstrate the existence of *CDK12* homozygous inactivation via copy-number alteration only, we included *CDK12* deep deletion in the definition of the *CDK12*-altered group. Future studies are needed to determine whether complete loss of *CDK12* can occur through deletion alone in prostate

cancer. *CDK12*-Bi inactivation in prostate cancer was associated with a higher prevalence of small-fragment copy-number alterations and a higher number of breakpoints across the genome, consistent with the previously described tandem duplicator phenotype [9,25], as tandem duplications are difficult to characterize directly using targeted panel sequencing assays. We found that *CDK12* mutations occur clonally in metastatic prostate cancer, and were identified in primary matched tumors from patients who developed metastatic disease, suggesting that *CDK12* loss of function is an early event in the pathogenesis of *CDK12*-altered metastatic prostate cancer. Our study differs from the pan-cancer analysis by Sokol et al. [15] in that we identified early occurrence of *CDK12* alterations in patients with matched tumors, and include a description of clinicopathologic features and clinical outcomes for prostate cancer patients, all within the same data set. Furthermore, our analysis of copy-number alterations in prostate tumors with *CDK12*-Bi inactivation compared with *CDK12*-WT tumors revealed numerous differentially altered regions. This includes amplification of 11q13.3, a region that encompasses the oncogene *CCND1*, and enrichment of alterations in cell-cycle pathway genes in patients with *CDK12* loss of function. We did not identify a significant co-occurrence of alterations in *CDK12* with DNA-repair gene alterations.

Identifying vulnerabilities of *CDK12*-altered prostate cancer is particularly important given our finding of somewhat more aggressive clinicopathologic features associated with *CDK12* alteration, including more aggressive disease at diagnosis, slightly shorter OS, and shorter time to castration resistance. A study in an independent cohort of 46 patients with *CDK12*-altered prostate cancer by Reimers et al. [16] recently revealed similar outcomes with regard to time to castration resistance and time on treatment with first-line abiraterone and enzalutamide. Our larger study differs in that it also showed shorter OS for patients with *CDK12*-altered cancer, and differences in outcomes were maintained after adjusting for common clinical prognostic variables, probably facilitated by the larger sample size, all within a single institutional data set using a single clinical tumor-sequencing assay. We noted a similar rate of Gleason 8–10 prostate cancer at diagnosis for patients with *CDK12*-altered disease in comparison to the Reimers study (80% vs 88%). One vulnerability of *CDK12*-altered prostate cancer may be a higher sensitivity to immune checkpoint blockade owing to the higher neoantigen burden resulting from the tandem duplicator phenotype associated with *CDK12* loss of function [9], a hypothesis that is currently being tested in a multi-institutional phase 2 study combining nivolumab with ipilimumab (NCT03570619). Of note, the slightly worse clinical outcomes we identified for *CDK12*-altered prostate cancer were unaffected by adjustment for FGA, suggesting that *CDK12* loss of function impacts disease behavior through a mechanism independent of broad copy-number changes, possibly by promoting genomic alterations in specific pathways, or by impacting gene expression through increased intronic polyadenylation [7]. Limitations of our study include its retrospective nature, the use of a targeted panel assay for genomic profiling, which can miss genomic rearrangements, and potential selection bias arising from the inclusion of patients only from a tertiary referral center.

5. Conclusions

In summary, our results suggest that *CDK12* loss of function defines a distinct subset of disease associated with unique genomic alterations and somewhat worse clinical outcomes, and highlights the need for novel therapies targeting *CDK12*-altered prostate cancer.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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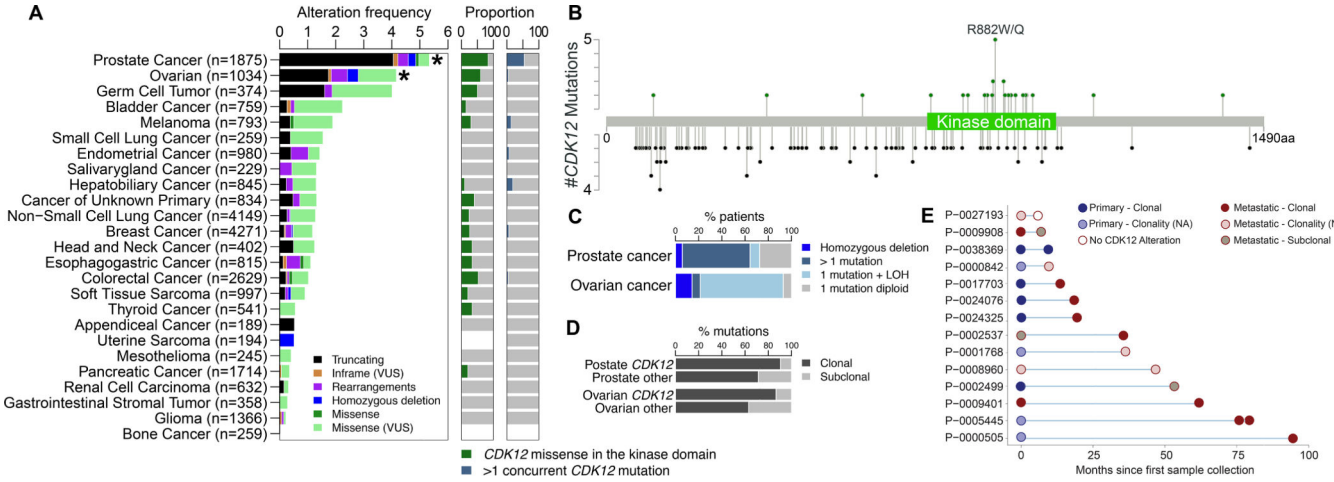

Fig. 1 –.

Landscape of somatic *CDK12* mutations across 25 cancer types in the MSK-IMPACT cohort. (A) Somatic *CDK12* alteration prevalence (left panel), proportion of kinase domain mutations among all missense mutations (middle panel), and proportion of cases with >1 *CDK12* mutation in an individual tumor (right panel) across 26743 tumors from 25 different cancer types. *CDK12* is significantly mutated in prostate and ovarian cancer only. * Significantly mutated according to MutSigCV. (B) Distribution of missense (upper green lollipop) and truncating mutations (lower black lollipop) in *CDK12* in prostate cancer. (C) Prevalence and type of biallelic inactivation of *CDK12* in prostate and ovarian cancer. (D) Prevalence of *CDK12* clonal mutations compared to all other mutations in prostate and ovarian cancer. (E) *CDK12* alterations in matched tumors in the prostate *CDK12* alteration cohort, including localized primaries and later metastases and other matched tumors from the same patients. LOH = loss of heterozygosity; NA = not evaluable.

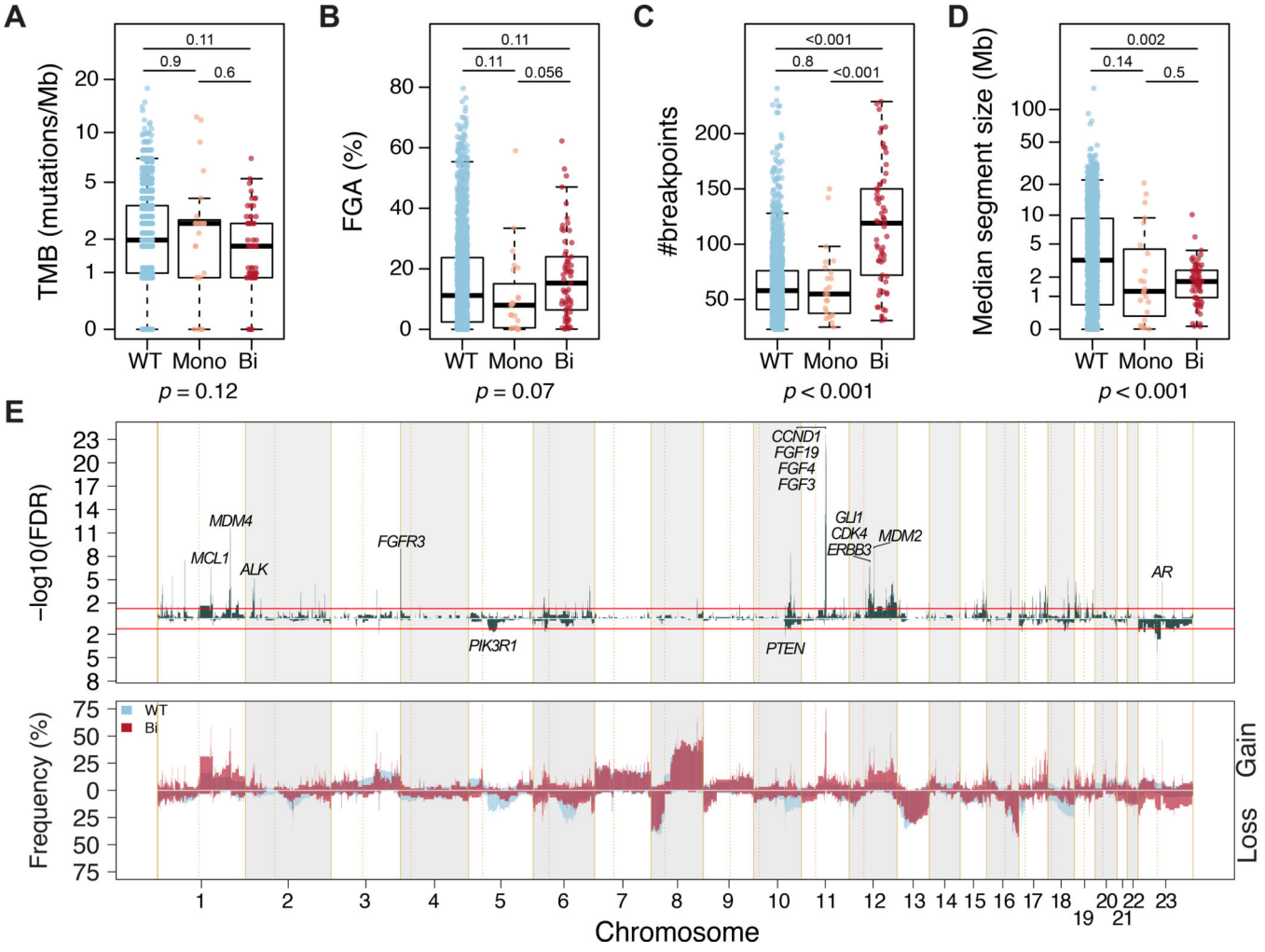

Fig. 2 –.

Genomic architecture of *CDK12*-altered prostate cancer. (A–D) Comparison of (A) tumor mutational burden (TMB), (B) fraction of genome altered (FGA), (C) number of breakpoints, and (D) median size of copy number alterations in prostate cancers with wild-type *CDK12* (WT, blue), *CDK12* with monoallelic inactivation (Mono, orange), or *CDK12* with biallelic inactivation (-Bi). The *p* values are derived from the Kruskal-Wallis H test. The *q* value (adjusted for multiple comparison) derived from the pairwise Mann-Whitney test is shown above each comparison. (E) Prevalence plot (bottom) and corresponding -log10(FDR) value derived from Fisher's exact test (top) comparing copy-number gains and losses between *CDK12*-WT (blue) and *CDK12*-Bi (red) prostate cancer. Selected oncogenic genes within affected chromosomal regions are shown. Red lines indicate FDR = 0.05. FDR = false discovery rate.

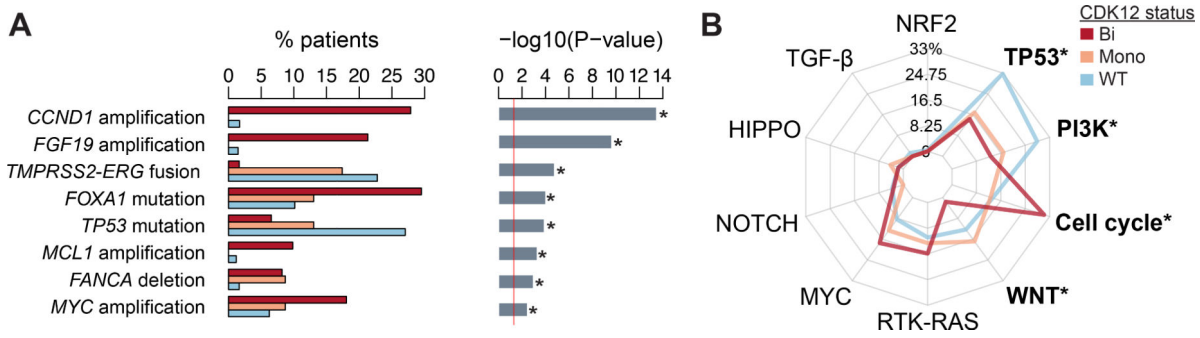

Fig. 3 –.

Oncogenic alterations associated with *CDK12*-altered prostate cancer. (A) Prevalence of recurrent oncogenic alteration in prostate cancer with *CDK12* biallelic (Bi, red) compared with *CDK12* monoallelic (Mono, orange) inactivation or *CDK12* wild-type tumors (WT, blue). The *p* values are derived from Fisher's exact test (* FDR < 0.05). (B) Radar plots showing the percentage of patients with alterations in the corresponding canonical oncogenic signaling pathways according to *CDK12* alterations. Statistically significant pathways associated with *CDK12* alteration are indicated with an asterisk (* FDR < 0.05). FDR = false discovery rate.

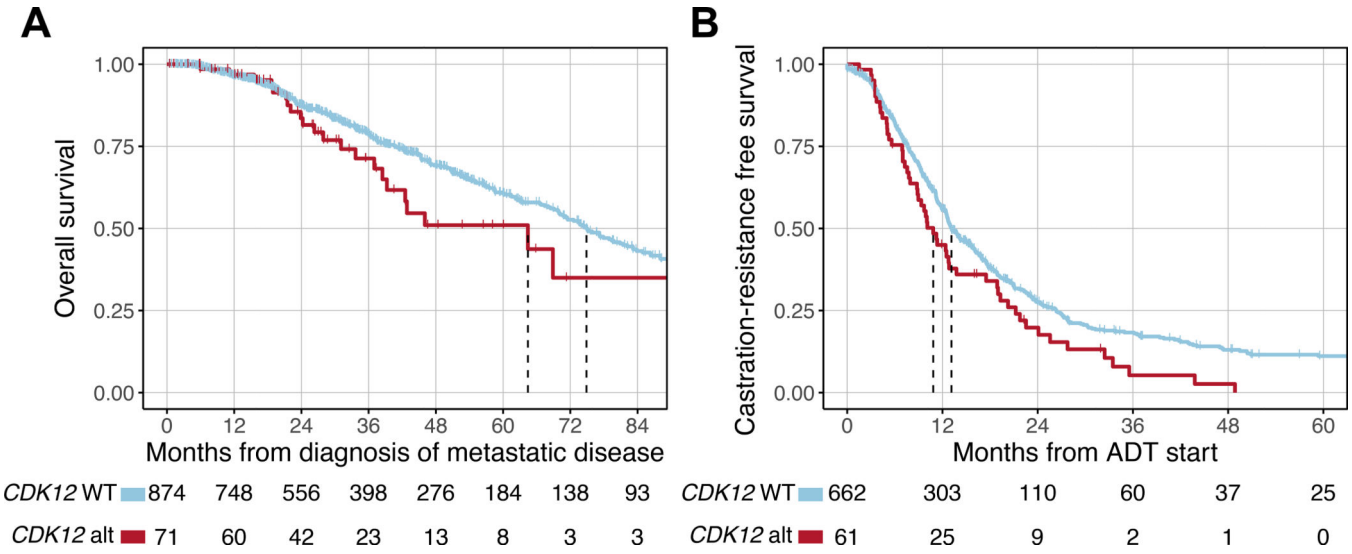

Fig. 4 –.

Clinical outcomes for *CDK12*-altered prostate cancer. (A) Overall survival from diagnosis of metastatic disease. (B) Time to development of castration-resistant prostate cancer from ADT initiation. ADT = androgen deprivation therapy.

Table 1:

Clinical and pathological characteristics of *CDK12*-altered and *CDK12*-WT prostate cancer patients

	***CDK12*-altered**	***CDK12*-WT**
Number of patients	100	1365
Age at diagnosis - years		
Median (IQR)	61 (54–67)	63 (56–68)
Histology at diagnosis - n (% of known cases)		
Adenocarcinoma	94 (97)	1216 (99)
Adenocarcinoma with neuroendocrine features	2 (2)	12 (0.9)
Other	1 (1)	6 (0.4)
Unknown	3	131
PSA at diagnosis - ng/mL		
Median (IQR)	14.8 (7.7–77.8)	9.0 (5.3–24.1)
Gleason - n (% of known cases)		
6	7 (8)	108 (9)
7	10 (12)	435 (34)
≥8	68 (80)	727 (57)
Not evaluable	15	95
Metastatic at diagnosis - n (% of known cases)	39 (40)	346 (26)
Unknown	2	23
Sites of metastasis at tissue collection - n (% of total metastatic patients)		
Bone	48 (60)	528 (57)
Nonregional lymph nodes	44 (55)	380 (41)
Liver	5 (6.3)	93 (10)
Lung	4 (5)	101 (11)
Visceral	7 (8.8)	165 (18)