Use of Circulating Tumor DNA for the Clinical Management of Metastatic Castration-Resistant Prostate Cancer: A Multicenter, Real-World Study

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ABSTRACT

Background: This study aimed to describe the aberrations of DNA damage repair genes and other important driving genes in Chinese patients with metastatic castration-resistant prostate cancer (mCRPC) using circulating tumor (ctDNA) sequencing and to evaluate the associations between the clinical outcomes of multiple therapies and key genomic alterations in mCRPC, especially DNA damage repair genes. **Patients and Methods:** A total of 292 Chinese patients with mCRPC enrolled from 8 centers. Multigene targeted sequencing was performed on 306 ctDNA samples and 23 matched tumor biopsies. The frequency of genomic alterations were compared with the Stand Up to Cancer–Prostate Cancer Foundation (SU2C-PCF) cohort. The Kaplan-Meier method was used to evaluate progression-free survival (PFS) following standard systemic treatments for mCRPC. Cox regression analyses were performed to determine prognostic factors associated with PFS resulting from treatments for mCRPC. **Results:** In total, 33 of 36 (91.7%) mutations were found consistently between ctDNA and paired biopsy samples. The most common recurrent genomic alterations were found in *AR* (34.6%), *TP53* (19.5%), *CDK12* (15.4%), *BRCA2* (13%), and *RB1* (5.8%). The frequency of *CDK12* alterations (15.4%) in our cohort was significantly higher than that in Western populations (5%–7%). *AR* amplification and *TP53* and/or *RB1* alterations were associated with resistance to abiraterone or docetaxel. Patients with a *CDK12* defect showed rapid disease progression after abiraterone treatment. However, the clinical outcome after docetaxel treatment was similar between patients with and without *CDK12* defects. In multivariate Cox regression analysis, a *CDK12* defect was significantly associated with inferior PFS after abiraterone treatment. Patients with a *BRCA2* defect showed marked response to both PARP inhibitors and platinum-based chemotherapy. **Conclusions:** Our study explored the genomic landscape of Chinese patients with mCRPC at different treatment stages using minimally invasive methods and evaluated the clinical implications of the driver genomic alterations on patients' response to the most widely used therapies for mCRPC. We observed a significantly higher alteration frequency of *CDK12* in our cohort compared with the SU2C-PCF cohort.

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Background

Metastatic castration-resistant prostate cancer (mCRPC) remains incurable, despite incremental improvements provided by multiple agents, including new-generation hormone therapies, taxane chemotherapy, and PARP inhibitors.[1–6] Genomic profiling of metastatic biopsies of mCRPC has revealed multiple molecular alterations, including alterations of DNA damage repair (DDR) genes, the androgen receptor (AR) gene, and the tumor suppressor genes *TP53* and *RB1*.[7] Previous studies preliminarily showed the prognostic relevance of these genes with multiple treatments in patients with mCRPC.[8–11] Despite this important advance in patient management, the understanding of mCRPC genetic epidemiology is mainly based on data from Western populations, with limited data available from other ethnicities. The large differences between Chinese and Western patients, especially in terms of their genomics, should not be ignored.[12,13] Whether these genetic alterations, especially those involving DDR genes, can predict the clinical outcomes of Chinese patients with mCRPC following specific treatments remains to be fully elucidated.

Routine sampling of bone and other metastatic tissues in patients with mCRPC is impractical. Therefore, the use of circulating tumor DNA (ctDNA) as a sample source for genomic analysis has gained momentum. ctDNA analysis is compatible with multiple sampling at different time points and can accurately capture tumor heterogeneity in a minimally invasive manner. Previous studies have

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shown substantial interpatient and intrapatient genomic heterogeneity in mCRPC.[7,14] In addition, the genomic profile of mCRPC is dynamic and evolves with systemic treatments, explaining its diverse molecular signatures at different treatment stages.[15,16]

Consequently, we hypothesized that ctDNA analysis could detect genomic alterations of mCRPC at different treatment stages and that these results might support its clinical utility in the standard-of-care setting. In the present study, we enrolled 292 patients with mCRPC from 8 centers in a real-world study and applied deep targeted ctDNA sequencing for an exploratory analysis of clinical implications.

Patients and Methods

Patients

This study was approved by the Committee for Ethics of Renji Hospital (approval number: [2016]115K), and informed consent was obtained from each of the 292 enrolled patients with mCRPC treated at Renji Hospital of Shanghai Jiaotong University School of Medicine, Shanghai Tenth People's Hospital, The First Affiliated Hospital of Wenzhou Medical University, Sun Yat-sen University Cancer Center, The First Affiliated Hospital of Xi'an Jiaotong University, Beijing Friendship Hospital, Fuzhou Central Hospital of Nanjing Military Command, and Zhejiang Provincial People's Hospital between December 2017 and December 2019. The study included 306 ctDNA samples and 23 matched biopsied tumor tissue samples (20 from the prostate, 2 from the liver, 1 from bone) collected at the same time. Among the 292 patients with mCRPC, 14 had 2 serial monitoring ctDNA samples and 23 had concurrent biopsied tumor tissue samples and ctDNA samples (supplemental eTable 1, available with this article at JNCCN.org). Clinical data were collected by the lead investigators at each site. Progression-free survival (PFS) was defined as the time from the date of treatment initiation to confirmed prostate-specific antigen (PSA) increase, clinical or radiographic progression, or death.

Target Capture and Sequencing

The targeted next-generation sequencing test of all samples was performed at GloriousMed Clinical Laboratory Co., Ltd. For blood samples, plasma was isolated by centrifugation at 1,600 × *g* for 10 minutes and then at 16,000 × *g* for 10 minutes. Cell-free DNA was extracted from 3 to 5 mL of plasma using a QIAamp Circulating Nucleic Acid Kit (Qiagen) according to the manufacturer's instructions. Tumor formalin-fixed paraffin-embedded (FFPE) DNA was extracted from 5 to 10 sections (5 mm thick) using a QIAamp DNA FFPE Tissue Kit (Qiagen), and genomic DNA was extracted from white blood cells using a Blood Genomic DNA Mini Kit (Cwbiotech). Two separate custom-designed DNA enrichment panels were used: The NimbleGen SeqCap EZ choice probe pool (Roche) was used to capture the coding regions of 620 or 642 genes, and the xGen Lockdown Probe Pool (Integrated DNA Technologies, Inc.) was used to capture the coding regions of 50 or 66 genes. To confirm concordance between the different gene panels used in the present study, 12 ctDNA samples were duplicated and sequenced from the 66-gene panel and the 620/642-gene panel. For analysis, we focused on the common 50 genes shown in supplemental eTable 2. For each sample, 20 to 100 ng of cell-free DNA, 200 to 500 ng of FFPE DNA, or 500 ng of genomic DNA were then used for library preparation and quantification, guided by KAPA Hyper Prep protocols (Kapa Biosystems, Inc.). Pools of 4 to 6 libraries were used to hybridize to the capture panel for 16 hours at 47°C for NimbleGen panel and at 65°C for xGen panel. Washing, recovery, and amplification were performed sequentially according the standard procedures of the NimbleGen SeqCap EZ and xGen panels. The libraries were then purified using AMPure XP (Beckman) and quantified using a Qubit dsDNA HS Assay Kit (ThermoFisher). The final libraries were sequenced on the Illumina Nextseq500 (75 bp paired-end reads) or the Novoseq6000 (150 bp paired-end reads) instruments (Illumina).

Quality Control and Variant Calling

Sequencing adapters were trimmed from the raw data using Trimmomatic.[17] The reads after adapter trimming were then aligned with the human reference genome using Burrows-Wheeler Alignment tool.[18] Duplicated reads were removed using Picard (http://broadinstitute.github.io/picard/). Mapped reads were also realigned to the genome using the Genome Analysis Toolkit (GATK).[19] Somatic and germline mutations were called using Mutect2 and the GATK Haplotype Caller[19] with a paired workflow, respectively. Variants were then annotated using ANNOVAR[20] and an in-house developed code. An in-house script was used to verify the human identity concordance of paired samples. Somatic copy number alterations were also detected using the GATK.[19]

Germline Variant Filtering

Germline variants called by the GATK on WBC samples were first filtered using a threshold of minimum coverage of 50× and an allele frequency of >30%. Variants not on coding regions and synonymous mutations annotated with ANNOVAR[20] were filtered out. Furthermore, variants with >0.1% population minor allele frequency annotated in the ExAC database (http://exac.broadinstitute.org/) were considered less functional and were ignored in the downstream analysis. Germline mutations considered deleterious (nonsense/stop-gains, frameshift insertions and deletions, and ± 1,2 splice-site variants, or those reported as pathogenic or likely pathogenic in the ClinVar database;

https://www.ncbi.nlm.nih.gov/clinvar/) were included for analysis.

Somatic Variant Filtering

Somatic mutations from ctDNA samples were filtered using the following rules: (1) 10 allele reads support, (2) 1% allele frequency, (3) supporting reads should be <4 in the WBC control, (4) mutation frequency should be 5 times higher than in the WBC control, (5) mutations should not occur more than twice in the panel of normals, and (6) no significant strand bias (GATK parameter FisherStrand annotation >60 for single-nucleotide polymorphisms and GATK parameter FisherStrand annotation >200 for insertions/deletions). Similar filtering rules were applied for somatic mutations from FFPE samples except for the allele frequency, which was required to be >5%, and the mutation frequency, which was required to be 8 times higher than that in the WBC control. Functional filtering removed variants located in noncoding regions, and synonymous mutations were removed for downstream analysis. A log2 ratio of >0.6 was considered a copy gain event for *AR*. A log2 ratio of <−0.7 was considered a copy loss.

Biallelic Inactivation Definition

Biallelic inactivation was defined as either homozygous deletion, ≥2 deleterious somatic mutations, 1 deleterious germline mutation with concurrent heterozygous loss of the wild-type allele, or 1 somatic mutation with loss of heterozygosity as computed using the FACETS algorithm.[21] Only samples with a ctDNA fraction ≥0.2 were used to infer biallelic inactivation.[22]

ctDNA Fraction Estimation

The mutant allele fraction (MAF) was first calculated using the somatic mutation profile from the sequencing results, followed by a correction model.[8] The ctDNA% was defined as $2/(1/\mathrm{MAF}+1)$ in diploid chromosomes as MAF, and ctDNA% was related as $\mathrm{MAF} = (\mathrm{ctDNA} \times 1)/[(1-\mathrm{ctDNA}) \times 2 + \mathrm{ctDNA} \times 1]$.

Statistical Analysis

All statistical analysis was conducted using R version 3.7 (R Foundation for Statistical Computing). The Fisher exact test was used to test the significance of differences for the somatic alterations between different groups. The Kaplan-Meier method was used to estimate the PFS of different treatments for patients, and differences between groups were analyzed using the log-rank test in the survival package (version 2.44-1.1). Univariate and multivariate Cox regression analyses were used to calculate their respective hazard ratios (HRs) and 95% confidence intervals. Only factors significant in univariate analyses were included in the subsequent multivariate analyses. A test result was considered as statistically significant for $P<.05$.

Results

Patient Characteristics

From the 8 institutions, 292 patients were recruited for analysis between December 2017 and December 2019 (supplemental eTable 3). Their baseline characteristics are summarized in Table 1. Median age before ctDNA sequencing was 69 years (interquartile range,

Table 1. Summary of Clinical Characteristics of 292 Patients With mCRPC (306 Samples)

Characteristic	Result
Median age at baseline (IQR), y	69 (65–76)
Gleason score	
6	7
7	54
8	77
9	82
10	28
Unknown	44
Median time from ADT initiation to mCRPC (IQR), mo	19 (11–30)
Unknown (n=39)	
PSA at time of ctDNA collected, n (%)	
>0–10 ng/mL	66 (21.6)
>10–20 ng/mL	42 (13.7)
>20–100 ng/mL	89 (29.1)
>100 ng/mL	96 (31.4)
Unknown	13 (4.2)
Site of metastatic cancer, n (%)	
Lymph node	273 (89.2)
Bone	280 (91.5)
Visceral	29 (9.5)
Received prior regimens for mCRPC at time of ctDNA collected, n (%)	
Treatment-naïve	93 (30.4)
First-line treatment of abiraterone	92 (30.1)
First-line treatment of docetaxel	40 (13.1)
Second-line or later-line treatment	81 (26.5)
Treatment of mCRPC after ctDNA collected, n (%)	
Abiraterone	58 (19.0)
Docetaxel	66 (21.6)
Platinum-based chemotherapy (post docetaxel)	19 (6.2)
Olaparib	27 (8.8)
Other	136 (44.4)
Median follow-up time (IQR), d	406 (285–550)

Abbreviations: ADT, androgen deprivation therapy; ctDNA, circulating tumor DNA; IQR, interquartile range; mCRPC, metastatic castration-resistant prostate cancer; PSA, prostate-specific antigen.

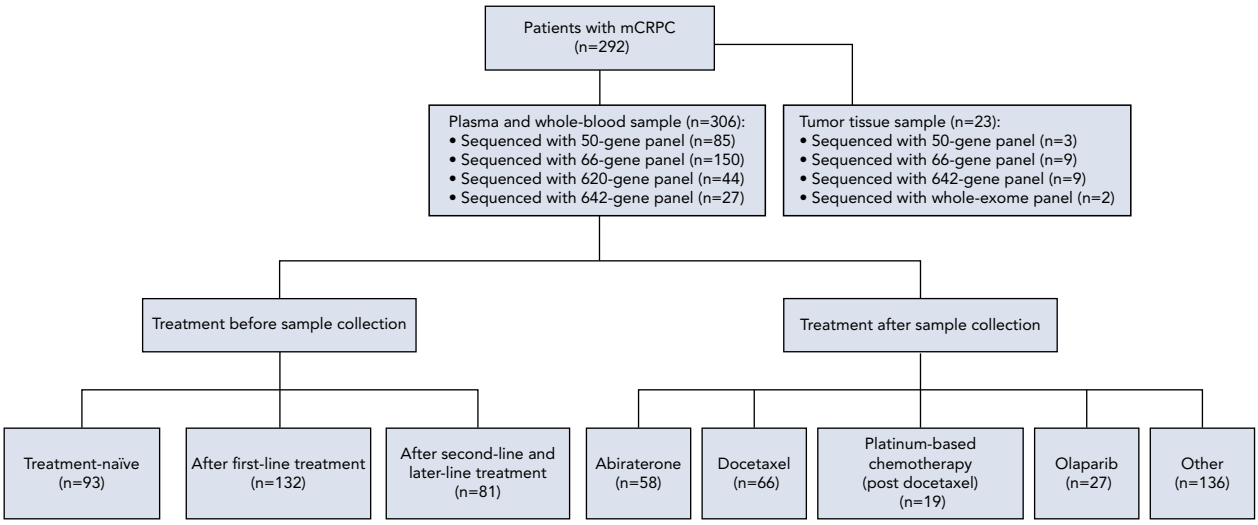

Figure 1. Flow diagram depicting the patients included in this cohort and patient groups according to treatments received before and after blood collection.
Abbreviation: mCRPC, metastatic castration-resistant prostate cancer.

65–76 years). The patients were categorized according to treatments received before blood collection. Among the 306 ctDNA samples, the patient numbers (proportion) of group A (treatment-naïve), group B (post first-line treatment of mCRPC), and group C (post second-line or later-line treatment of mCRPC) were 93 (30.4%), 132 (43.1%), and 81 (26.5%), respectively. Patients were also categorized according to treatment after blood collection. Baseline sample numbers from those receiving treatment (after baseline ctDNA collection) were as follows: abiraterone (n=58), docetaxel (n=66), platinum-based chemotherapy post docetaxel (n=19), olaparib (n=27), and other treatments (n=136) (Figure 1).

Mutational Concordance Between Tumor Tissue and ctDNA

Twenty-three patients with ctDNA samples also had paired tumor biopsy tissues available (20 from the prostate, 2 from the liver, 1 from the bone, collected at the same time). Among these 23 patients, 5 had no detectable somatic mutations in either the ctDNA or the tissue sample. For the remaining 18 patients, 54 and 36 somatic mutations were identified in ctDNA samples and the corresponding tumor tissue samples, respectively. In total, 33 of 36 (91.7%) mutations were found consistently between ctDNA and tissue samples (Figure 2A, supplemental eTable 4). All *CDK12* mutations identified in tissue samples were found in ctDNA. Among the 24 mutations detected in 1 sample type but not in the other (ie, discordant mutations), 3 were present in tumor tissues but absent in ctDNA (*FOXA1* S436fs, *RB1* P29fs, *PALB2* L708X) and 21 were unique to ctDNA, including mutations in *AR*, *BRCA2*, *ATM*, *PTEN*, and *TP53* (Figure 2B).

As the sequencing platform evolved, different targeted gene sequencing panels were used in the present study. To confirm the concordance between different gene panels, 12 ctDNA samples were duplicated and subjected to tests with the 66-gene and 620/642-gene panels. All somatic mutations detected using the 620/642-gene panel were confirmed using the 66-gene panel, with remarkably consistent allele fractions (supplemental eFigure 1A). Copy number calls in 4 driver genes (*AR*, *BRCA2*, *CDK12*, and *TP53*) of mCRPC were also concordant between the 2 DNA capture panels (supplemental eFigure 1B).

Genomic Landscape of Chinese Patients With mCRPC

Somatic and deleterious germline alterations were identified in 201 of 292 patients (for the 14 patients with serial samples, data from the first sample were used) (supplemental eFigure 2A, B and eTable 5). In total, 43.2% of patients carried alterations of homologous recombination repair (HRR) genes and 6.85% harbored alterations in mismatch repair genes. Among the top 3 altered HRR genes, *CDK12* (15.4%) alterations were exclusively somatic events, and alterations in *BRCA2* (13%) and *ATM* (7.5%) were either in the germline or somatic (supplemental eFigure 2B, C, D). Among the patients with a ctDNA fraction >20%, biallelic inactivation occurred in 62.5% (10/16), 73.9% (17/23), and 44.4% (4/9) of *BRCA2*, *CDK12*, and *ATM*, respectively. Compared with other DDR genes (including *BRCA1*, *BRCA2*, *ATM*, *MLH1*, and *MSH2*), the proportion of *CDK12* mutations (15.4%) was significantly higher than reported previously in the Stand Up to Cancer–Prostate Cancer Foundation (SU2C-PCF) cohort (supplemental eFigure 3).

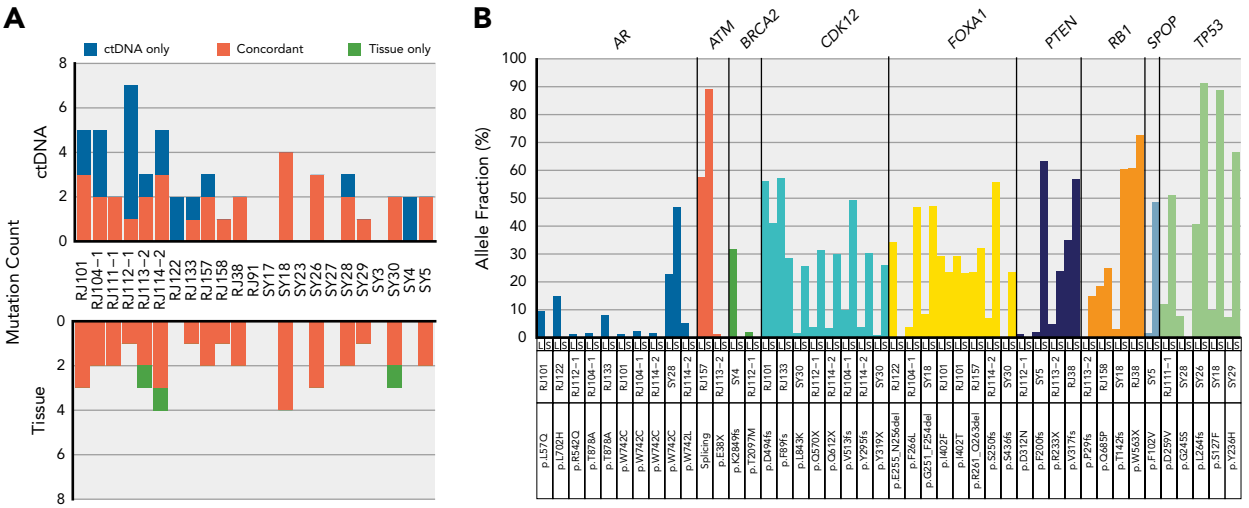

Figure 2. Concordance of mutation calls between ctDNA samples and paired tumor tissues in 23 patients. (A) Somatic mutation count of ctDNA and tumor tissues. (B) Variant allele frequencies for selected driven mutations between matched liquid cell tumor DNA and solid tumor tissue. Abbreviations: ctDNA, circulating tumor DNA; L, liquid cell tumor DNA; S, solid tumor tissue.

According to the number of prior therapies before sampling, the 306 samples from the 292 patients were divided into 3 groups: treatment-naïve (group A; n=93), post first-line treatment (group B; n=132), and post second-line or later-line treatment (group C; n=81). The somatic alteration patterns in these subgroups are shown in Figure 3A. Alterations in *AR* increased progressively from group A (21.5%) to group B (37.1%) to group C (46.9%) (*P*<.001). Likewise, the frequency of *TP53* alterations increased significantly in group C (24.7%) compared with group A (12.9%) (*P*=.035) (Figure 3B). The somatic profile of 14 patients with 2 serial ctDNA samples is shown in supplemental eFigure 4.

Somatic Alterations of *CDK12*, *TP53*, and/or *RB1* Associated With Outcomes of Abiraterone

Among patients with ctDNA collected before abiraterone treatment (n=58), the PSA response (>50% decline) in 12 weeks was observed in 27 patients (46.55%) (Figure 4A, supplemental eTable 6). Only 1 (14.29%) of 7 patients with *CDK12* defects achieved a PSA response. None of the patients with *TP53* or *RB1* defects (n=8) achieved a PSA response. No significant difference in PFS was observed between patients with and without *BRCA2* or *ATM* defects in the abiraterone-treated group (supplemental eFigure 5A, B). *CDK12* defects were associated with shorter PFS after abiraterone treatment (1.6 vs 10.4 months; *P*=.001) (Figure 4B). Patients with *TP53* or *RB1* defects had a significantly shorter PFS than those without these defects after abiraterone treatment (2.0 vs 11.0 months; *P*<.001) (supplemental eFigure 5C). Median PFS for patients receiving abiraterone treatment was 3.0 months for those with *AR* gain (n=5) compared with 10.4 months in those without *AR* gain (*P*=.007) (supplemental eFigure 5D). No significant difference in median PFS was observed between patients with and without *AR* mutations (supplemental eFigure 5E).

In univariate analysis, 6 variables were significantly associated with PFS after abiraterone treatment (Table 2). In multivariable analysis, after adjusting for clinical factors, mutation classification, and therapeutic information (Table 2), *CDK12* defects (HR, 19.587; 95% CI, 3.788–101.278; *P*<.001), *TP53* or *RB1* defects (HR, 4.727; 95% CI, 1.554–14.383; *P*=.006), and visceral metastasis (HR, 10.827; 95% CI, 2.386–49.119; *P*=.002) remained significant.

Somatic Alterations of *TP53* and/or *RB1* Associated With Outcomes of Docetaxel

Among patients with ctDNA collected before docetaxel-only treatment (n=66), a PSA response in 12 weeks was observed in 29 patients (43.94%) (Figure 4C, supplemental eTable 7). A total of 4 (40%) of 10 patients with *CDK12* defects achieved a PSA response, and 2 (20%) of 10 patients with *TP53* or *RB1* defects achieved a PSA response. No significant difference in median PFS was observed between patients with and without *CDK12*, *BRCA2*, or *ATM* defects (Figure 4D, supplemental eFigure 6A, B). Patients with *TP53* or *RB1* defects had a significantly shorter PFS than those without *TP53* or *RB1* defects after docetaxel treatment (4.8 vs 8.0 months; *P*=.019; supplemental eFigure 6C). Median PFS for patients receiving docetaxel treatment was 5.0 months for those with *AR* gain compared with 8.0 months in those without *AR* gain (*P*=.012) (supplemental eFigure 6D).

In univariate analysis, 4 variables were significantly associated with PFS after docetaxel treatment (Table 2).

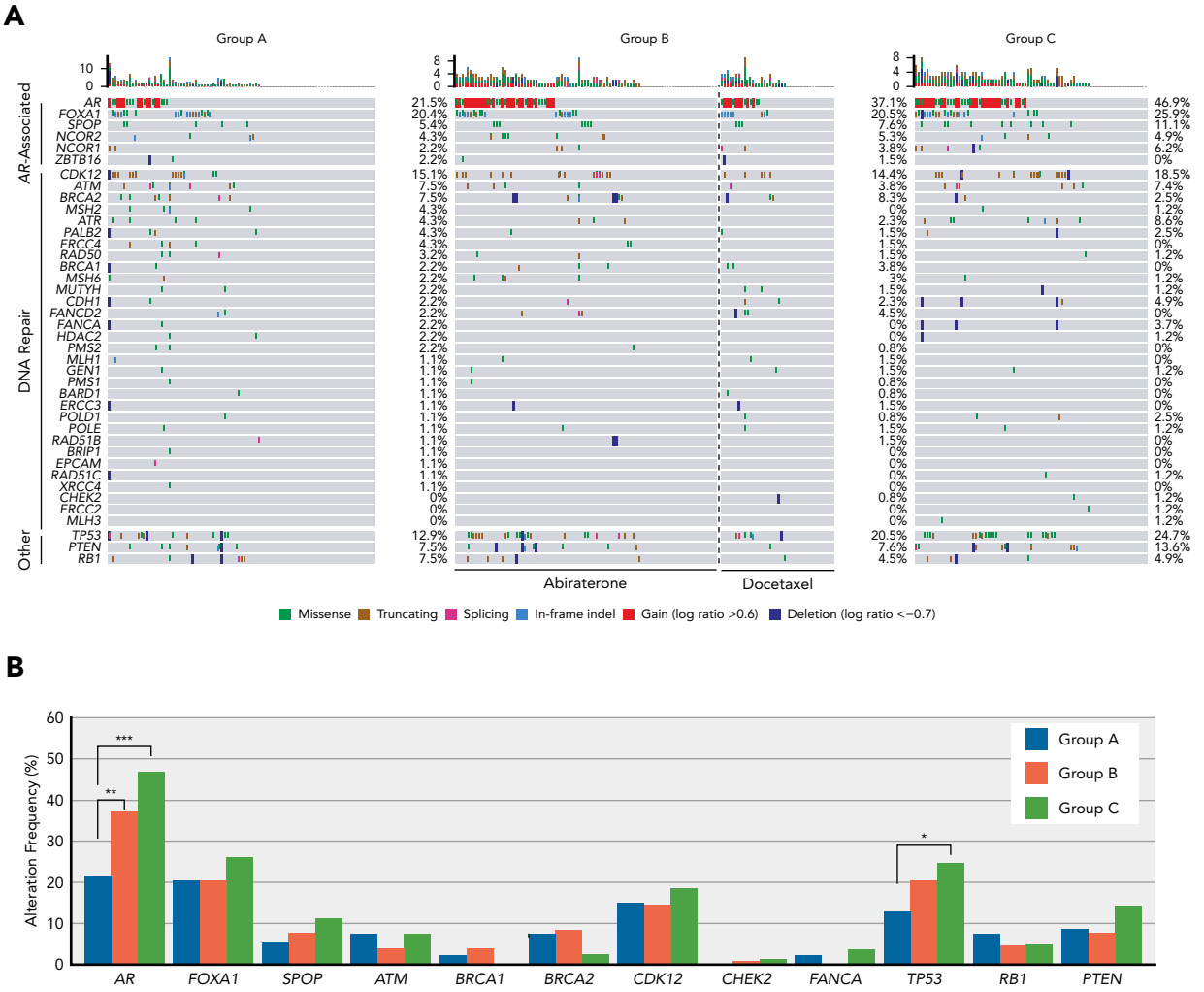

Figure 3. Somatic genomic alterations across different treatment stage groups for mCRPC. (A) Somatic alterations in patients stratified into 3 groups based on prior number of mCRPC systemic treatments: group A (treatment-naïve; n=93), group B (post first-line treatment with abiraterone or docetaxel; n=132), and group C (post second-line or later-line treatment; n=81). (B) Comparison of frequency of somatic alteration in selected genes from the 3 groups based on prior number of treatments.

Abbreviations: indel, insertions/deletions; mCRPC, metastatic castration-resistant prostate cancer.

*P<.05; **P<.01; ***P<.001.

In multivariable analysis, after adjusting for clinical factors, mutation classification, and therapeutic information (Table 2), *TP53* or *RB1* defects (HR, 2.805; 95% CI, 1.130–6.965; P=.026), PSA level (>100 vs ≤100 ng/mL; HR, 2.731; 95% CI, 1.418–5.262; P=.003), and visceral metastasis (HR, 11.517; 95% CI, 2.348–56.503; P=.003) showed statistical significance.

DDR Genes May Help Predict Efficacy of Platinum-Based Chemotherapy and PARP Inhibitors

Nineteen patients were sequenced before platinum-based chemotherapy, and 3 of these discontinued treatment after 1 cycle of cisplatin or carboplatin because of serious adverse effects. Of these 16 patients, 8 showed deleterious alterations in DDR genes (supplemental eTable 8). PSA changes at 12 weeks for each patient during platinum-based chemotherapy are displayed in supplemental eFigure 7A. Of the 8 patients with a DDR defect, 7 (87.5%) had a PSA decline (including 1 patient with a *CDK12* defect) and 6 (75%) had a PSA decline >50%. Conversely, in the 8 patients who had no PSA decline, only 1 harbored an *ERCC3* alteration and the remaining 7 had no detectable alteration of DDR genes.

Median PFS after platinum-based chemotherapy in patients with a DDR gene defect was significantly longer than for those without a DDR gene defect (12.0 vs 2.0 months; P=.002; supplemental eFigure 8A). Patients with *BRCA2* defects had a median PFS of 12 months (95% CI, 11.0–not available), compared with 13 months in patients

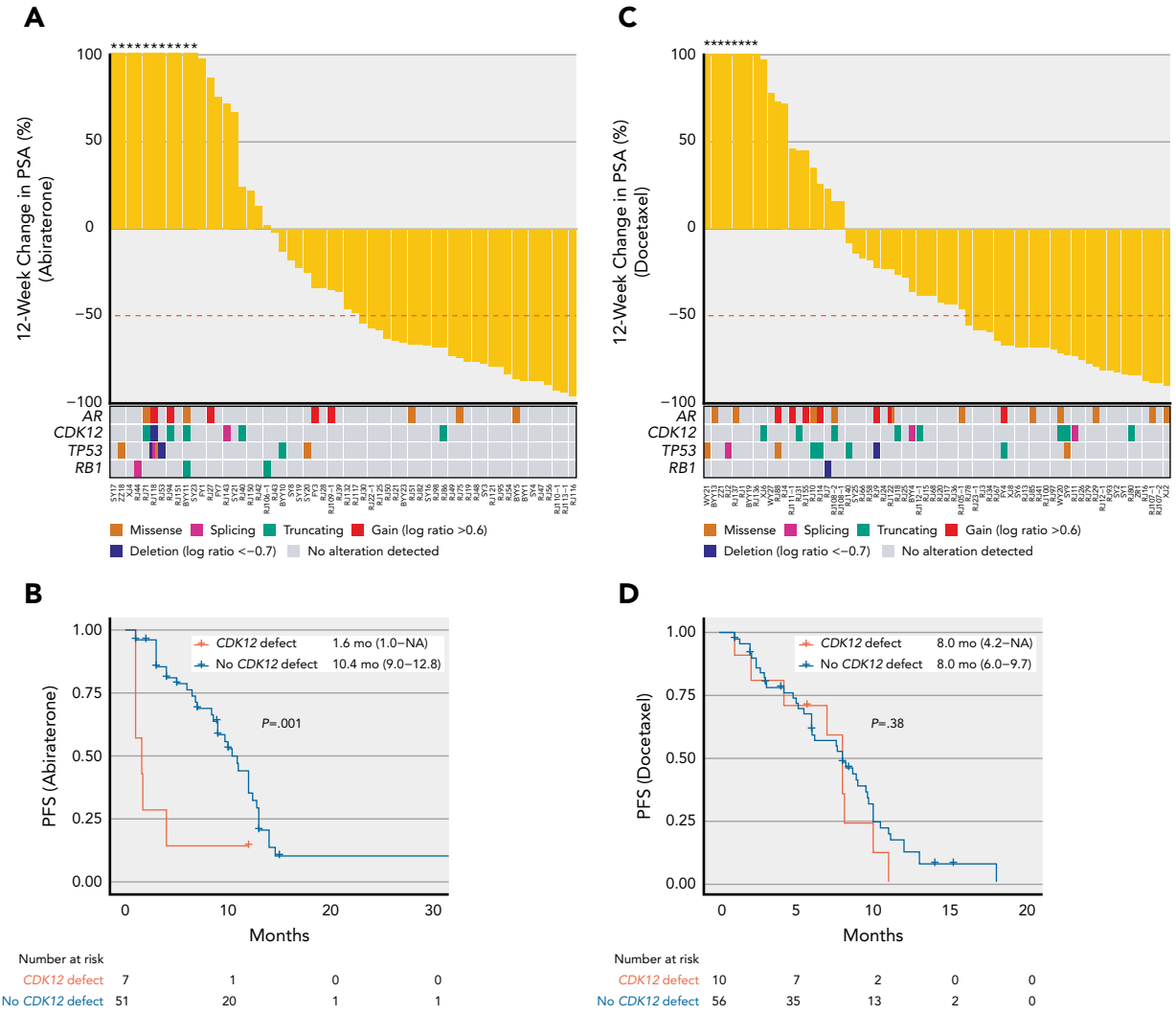

Figure 4. Association between genomic alterations and clinical outcomes of abiraterone or docetaxel. (A) Waterfall plot for percent PSA change in response to abiraterone in 12 weeks. (B) Kaplan-Meier curves for PFS in patients with and without a *CDK12* defect in the abiraterone treatment group. (C) Waterfall plot for percent PSA change in response to docetaxel in 12 weeks. (D) Kaplan-Meier curves for PFS in patients with and without a *CDK12* defect in the docetaxel treatment group. The asterisk (*) above each bar indicates that it was truncated.
Abbreviations: NA, not available; PSA, prostate-specific antigen; PFS, progression-free survival.

with other DDR defects and 2.0 months in those with no DDR defect (P=.008; supplemental eFigure 8B).

A total of 27 patients in the entire cohort received olaparib, including 5 who were lost to follow-up; 10 revealed no defect in DDR genes, whereas 12 of 22 patients had DDR gene defects (supplemental eTable 9), and PSA responses were observed in 5 (41.7%) of these 12 patients. All 4 patients with *BRCA2* defects had a PSA level decline, 3 (75%) of whom achieved a PSA response, and 1 (25%) of the 4 patients with *CDK12* defects achieved a PSA response (supplemental eFigure 7B). There was no significant difference in median PFS between patients with and without DDR gene defects (4.0 vs 1.8 months; P=.19; supplemental eFigure 8C). The median PFS of patients receiving olaparib was 10.7 months for those with *BRCA2* defects (n=4) compared with 2.9 months for those with other DDR gene defects (including *ATM* and *CDK12* defects; n=8) and 1.8 months for those without detectable DDR gene defects (n=10; P=.1; supplemental eFigure 8D).

Discussion

This was a real-world multi-institutional study that explored the genomic landscape of Chinese patients with mCRPC at different treatment stages and evaluated the relevance of ctDNA targeted sequencing with treatments for mCRPC. First, we found that *CDK12* alterations (15.4%) in our Chinese CRPC cohort were significantly more frequent than in Caucasian patients. In addition,

Table 2. Univariate and Multivariate Analyses of Various Prognostic Parameters in PFS Using Abiraterone and Docetaxel

	Abiraterone-Treated Group (n=58)				Docetaxel-Treated Group (n=68)			
	Univariate Analyses		Multivariate Analyses		Univariate Analyses		Multivariate Analyses	
	HR (95% CI)	*P* Value	HR (95% CI)	*P* Value	HR (95% CI)	*P* Value	HR (95% CI)	*P* Value
PSA level (>100 vs ≤ 100 ng/mL)	6.472 (2.172–19.282)	.001	5.938 (0.778–45.296)	.086	2.172 (1.168–4.041)	.014	2.731 (1.418–5.262)	.003
Gleason score (≤7 vs >7)	1.086 (0.555–2.126)	.81	—	—	0.858 (0.454–1.621)	.637	—	—
Treatment-naïve vs posttreatment	1.199 (0.598–2.404)	.61	—	—	1.001 (0.572–1.751)	.997	—	—
Visceral metastasis vs no visceral metastasis	5.582 (1.745–17.860)	.004	10.827 (2.386–49.119)	.002	7.185 (1.581–32.657)	.011	11.517 (2.348–56.503)	.003
Time from ADT initiation to mCRPC (≤12 vs >12 mo)	2.436 (1.100–5.392)	.028	1.522 (0.591–3.922)	.385	0.952 (0.523–1.732)	.867	—	—
CDK12 defect vs no *CDK12* defect	3.877 (1.568–9.585)	.003	19.587 (3.788–101.278)	<.001	1.377 (0.664–2.854)	.39	—	—
AR amplification vs no *AR* amplification	3.910 (1.294–11.281)	.016	1.484 (0.184–11.976)	.711	2.968 (1.210–7.277)	.017	1.375 (0.459–4.117)	.569
AR pathogenic mutation vs no *AR* pathogenic mutation	1.523 (0.592–3.915)	.383	—	—	0.687 (0.308–1.533)	.359	—	—
TP53 or *RB1* defect vs no *TP53* or *RB1* defect	7.401 (2.935–18.665)	<.001	4.727 (1.554–14.383)	.006	2.328 (1.112–4.875)	.025	2.805 (1.130–6.965)	.026
BRCA2 defect vs no *BRCA2* defect	0.719 (0.220–2.346)	.584	—	—	1.327 (0.615–2.866)	.471	—	—
ATM defect vs no *ATM* defect	1.613 (0.382–6.811)	.515	—	—	1.305 (0.314–5.426)	.715	—	—

Abbreviations: ADT, androgen deprivation therapy; HR, hazard ratio; mCRPC, metastatic castration-resistant prostate cancer; PSA, prostate-specific antigen; PFS, progression-free survival.

we found that *CDK12* defect had a predictive role in mCRPC's response to multiple treatments, including abiraterone and docetaxel chemotherapy, which may help guide treatment selection in mCRPC. Third, we found that DDR genes, especially *BRCA2*, detected by ctDNA targeted sequencing may help predict the efficacy of platinum-based chemotherapy and PARP inhibitors.

Recently, a novel molecular subtype of advanced prostate cancer harboring *CDK12* mutations was reported in patients with mCRPC.[7,23–27] In a whole-exome sequencing study of 150 metastatic biopsies, the SU2C-PCF International Consortium identified DDR gene inactivation in 23% of patients, with *BRCA2* defects being the most common (12%).[7] Previous studies in Western populations reported that the frequency of *CDK12* mutations was 5% to 7%.[7,8,14] In our cohort of Chinese men with mCRPC, the most frequently altered gene among the DDR genes was *CDK12* (15.4%), which was almost double that observed in Western populations with mCRPC.[7,8,14] By contrast, the alteration frequencies of *BRCA1*, *BRCA2*, and *ATM* were more in line with the SU2C-PCF International Consortium data.[7] *CDK12* functions in DNA transcription and RNA splicing, regulates DDR genes involved in HRR, and has been suggested to increase susceptibility to PARP inhibitors.[28–31] More recently, studies have shown that *CDK12*-mutated prostate cancer had different molecular characteristics[23] with aggressive clinical behaviors.[25,32,33] Biallelic inactivation of *CDK12* in prostate cancer is associated with elevated neoantigen burden and increased tumor T-cell infiltration/clonal expansion, resulting in sensitivity to immune checkpoint inhibitors.[24] However, the clinical outcomes of *CDK12*-mutated prostate cancer using standard systemic therapies remain controversial.[25,32,33] Our data support that *CDK12* had a predictive role in mCRPC's response to multiple treatments, including abiraterone and docetaxel chemotherapy. *CDK12* defects were associated with worse efficacy after abiraterone treatment, whereas the clinical outcome after docetaxel treatment was similar between patients with and without *CDK12* defects. Further studies will assess how *CDK12* defects are involved in the resistance or sensitivity to multiple therapies in mCRPC.

Emerging evidence suggests that DDR-associated prostate cancer has an impressive response to platinum-based chemotherapy.[34–36] In this study, we observed that 7 patients experienced a PSA response, and 6 of them (85.7%) had deleterious alterations in DDR genes (3 with

somatic *BRCA2* defects). Conversely, of the 8 patients who had no PSA decline, 7 had no detectable alteration of DDR genes. We also found that the median PFS after platinum-based chemotherapy in patients with DDR defects was significantly longer than in those without a DDR defect.

Recently, the FDA approved PARP inhibitors to treat HRR gene–mutated mCRPC. Our results suggest that not all DDR gene defects are equally predictive of a PARP inhibitor response. Patients with *BRCA2* defects experienced superior outcomes compared with those with other DDR defects, which is consistent with previous reports.[37,38] This finding suggests that when considering PARP inhibitor treatment in patients with mCRPC, it is necessary to carefully examine the established functional association of changes in DDR genes, especially in genes other than *BRCA2*.

AR amplification was reported to indicate worse efficacy of the *AR* signaling pathway inhibition (ARPI) in previous studies.[8,9] Our results are consistent with the conclusions made in those studies. Previous analyses have also suggested that mutational loss of *TP53* and *RB1* may predict poor survival in patients with mCRPC treated using ARPI.[8,9] Loss of *TP53* and *RB1* is frequently observed in lethal prostate cancer and has been correlated with lineage plasticity and the formation of neuroendocrine differentiation in prostate cancer,[39,40] which explains primary resistance to ARPI. However, the association between *TP53* or *RB1* defects and the efficacy of docetaxel had not been examined previously. Our results showed that patients with mCRPC with *TP53* and/or *RB1* defects were associated with rapid resistance to both abiraterone and docetaxel.

Our study has several limitations. Although the high concordance between tumor tissue and ctDNA has been shown and liquid biopsies may capture tumor heterogeneity, they may fail to detect ctDNA in patients with a low disease burden and may have included low-frequency mutations from clonal hematopoiesis. In addition, the panels used in the study only capture exon regions, and therefore some meaningful intron mutations could be missing. Moreover, because of the small sample size in each treatment subgroup, clinical outcomes of the biallelic versus monoallelic mutations of key genes in patients with prostate cancer were not compared. Thus, the correlation between mutational status and treatment response should be interpreted with caution. The predictive value of specific genes and clinical benefit of the ctDNA test must be confirmed by additional prospective studies.

Conclusions

Our study explored the genomic landscape of Chinese patients with mCRPC at different treatment stages using minimally invasive methods and evaluated the clinical implications of the driver genomic alterations on the patients' response to the most widely used therapies for mCRPC. We observed a significantly higher alteration frequency of *CDK12* in our cohort compared with the SU2C-PCF cohort.[7]

Acknowledgments

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Supplemental online content for:

Use of Circulating Tumor DNA for the Clinical Management of Metastatic Castration-Resistant Prostate Cancer: A Multicenter, Real-World Study

Baijun Dong, PhD; Liancheng Fan, MD; Bin Yang, MD, PhD; Wei Chen, MD; Yonghong Li, MD; Kaijie Wu, MD, PhD; Fengbo Zhang, MD; Haiying Dong, MD, PhD; Huihua Cheng, MBBS; Jiahua Pan, MD; Yinjie Zhu, MD; Chenfei Chi, MD; Liang Dong, MD; Jianjun Sha, MD; Lei Li, MD, PhD; Xudong Yao, MD; and Wei Xue, MD

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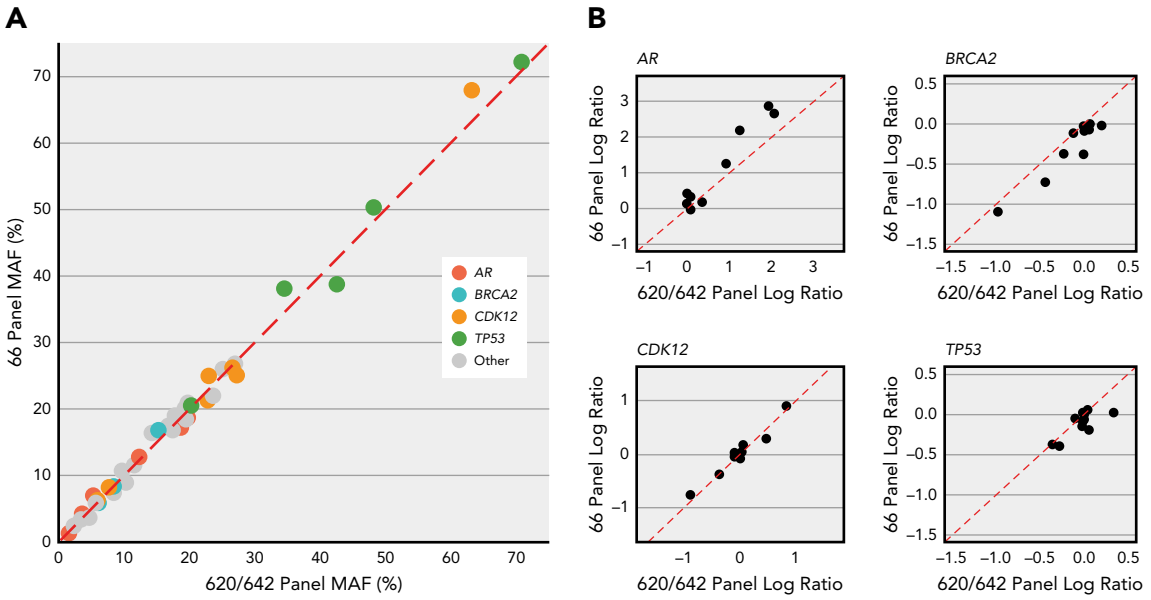

eFigure 1. Concordance between genomic alterations detected using the 620/642-gene and the 66-gene panels. (A) Scatterplot showing MAF measured using the 2 panels. All mutations detected using the 66-gene panel are shown. (B) Scatterplots showing coverage log ratios measured using the 2 panels for 4 driver genes of mCRPC. Each dot represents a ctDNA sample whose sequence was present in both panels.
Abbreviations: ctDNA, circulating tumor DNA; MAF, mutant allele fraction; mCRPC, metastatic castration-resistant prostate cancer.

eFigure 2. Genomic alterations of 292 patients with mCRPC assessed using targeted ctDNA sequencing. (A) Genomic landscape of non-synonymous somatic mutations and deleterious germline mutations. Genes grouped by relevant pathways are represented on the left. The frequency of alteration of each gene is provided on the right. The type of alteration is denoted in the row below. (B) The frequency of somatic and deleterious germline alterations in selected actionable genes such as *AR, BRCA2, ATM, CDK12, TP53, and RB1*. (C) Oncoprint of somatic and deleterious germline alterations in *AR, BRCA2, ATM, CDK12, TP53, and RB1*. (D) Location of somatic and deleterious germline mutations in *AR, BRCA2, ATM, CDK12, TP53, and RB1*.

Abbreviations: ctDNA, circulating tumor DNA; indel, insertions/deletions; mCRPC, metastatic castration-resistant prostate cancer.

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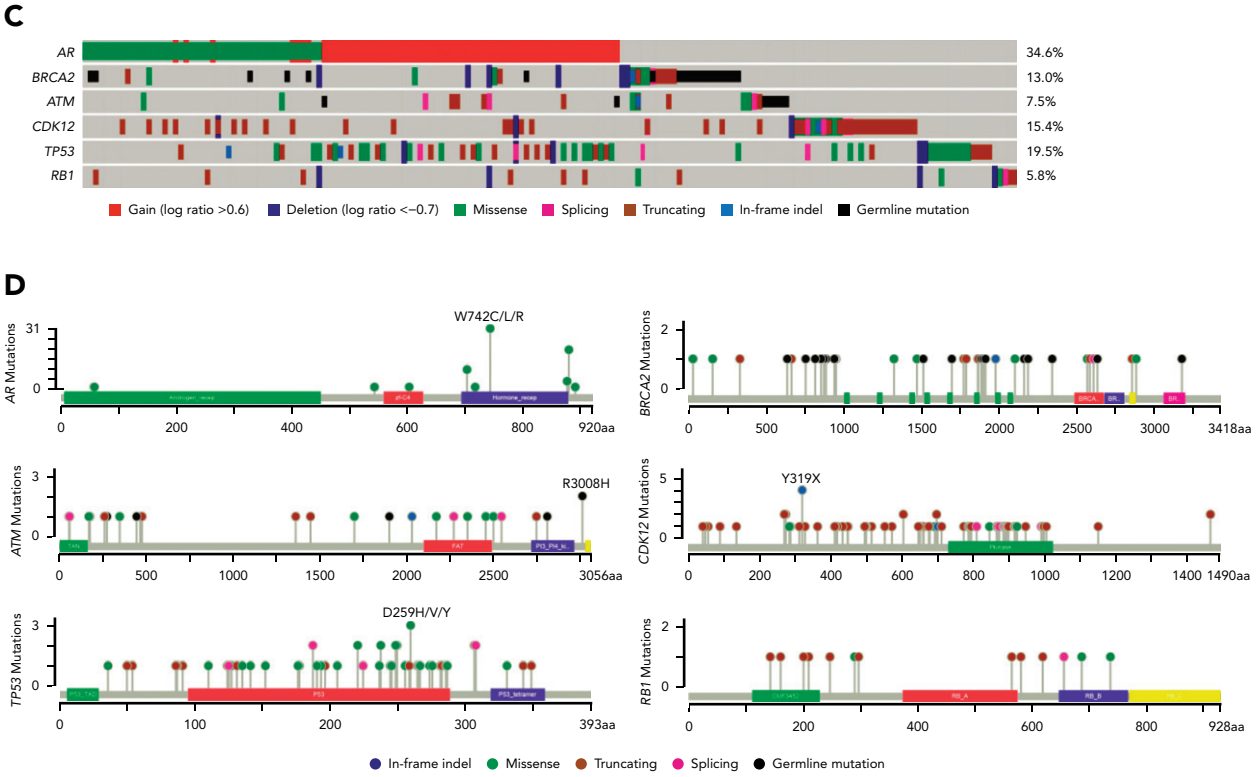
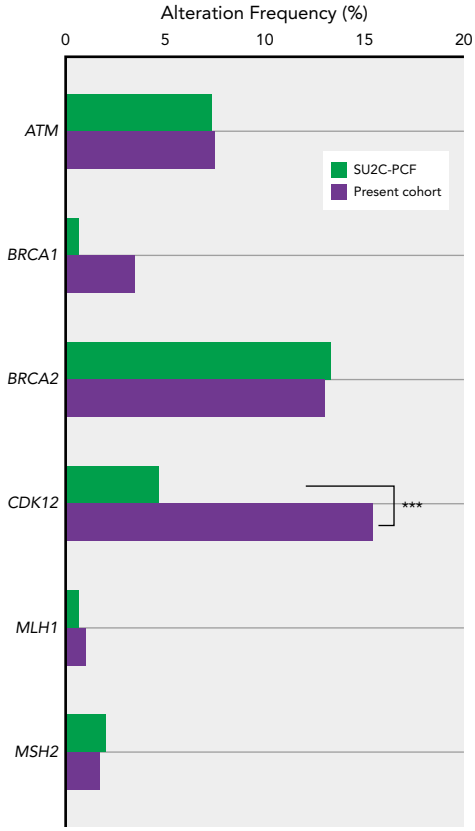
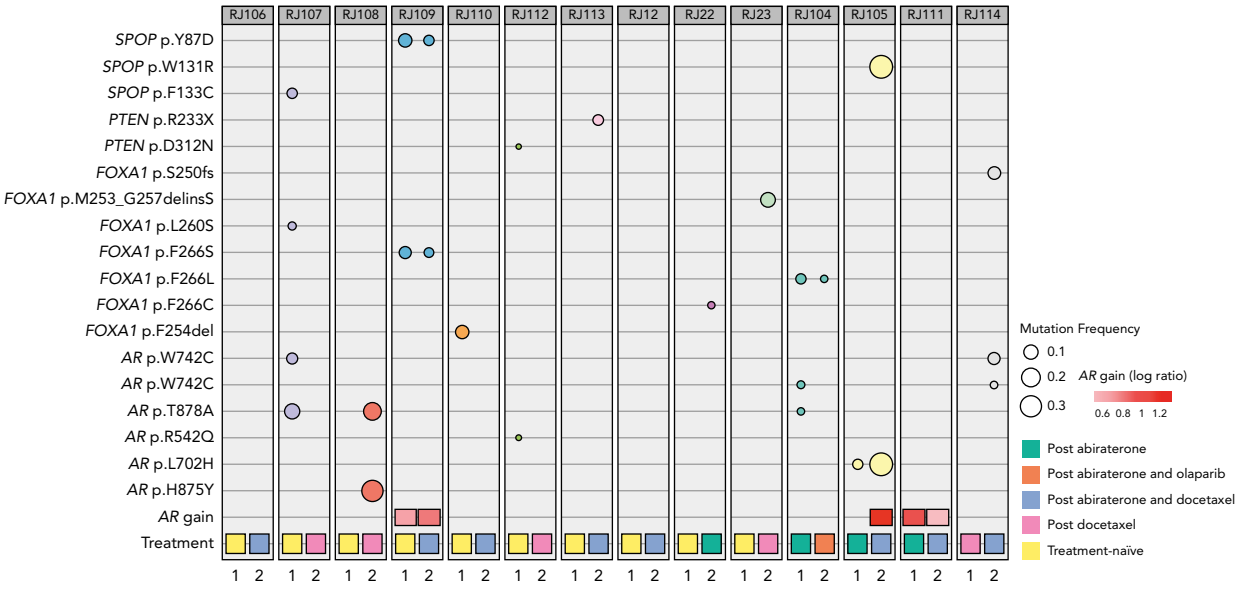


eFigure 2 (cont.). Genomic alterations of 292 patients with mCRPC assessed using targeted ctDNA sequencing. (A) Genomic landscape of nonsynonymous somatic mutations and deleterious germline mutations. Genes grouped by relevant pathways are represented on the left. The frequency of alteration of each gene is provided on the right. The type of alteration is denoted in the row below. (B) The frequency of somatic and deleterious germline alterations in selected actionable genes such as *AR*, *BRCA2*, *ATM*, *CDK12*, *TP53*, and *RB1*. (C) Oncoprint of somatic and deleterious germline alterations in *AR*, *BRCA2*, *ATM*, *CDK12*, *TP53*, and *RB1*. (D) Location of somatic and deleterious germline mutations in *AR*, *BRCA2*, *ATM*, *CDK12*, *TP53*, and *RB1*.

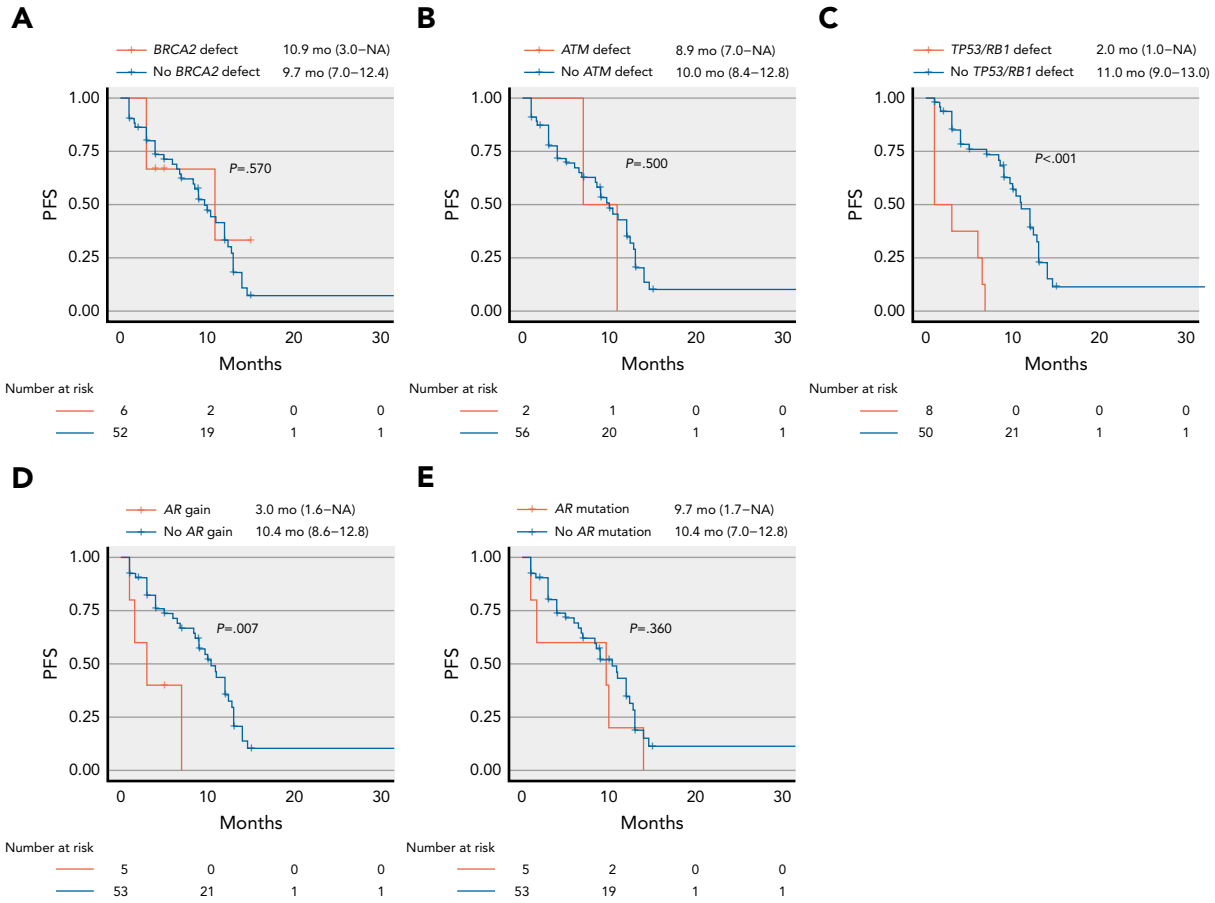
Abbreviations: ctDNA, circulating tumor DNA; indel, insertions/deletions; mCRPC, metastatic castration-resistant prostate cancer.



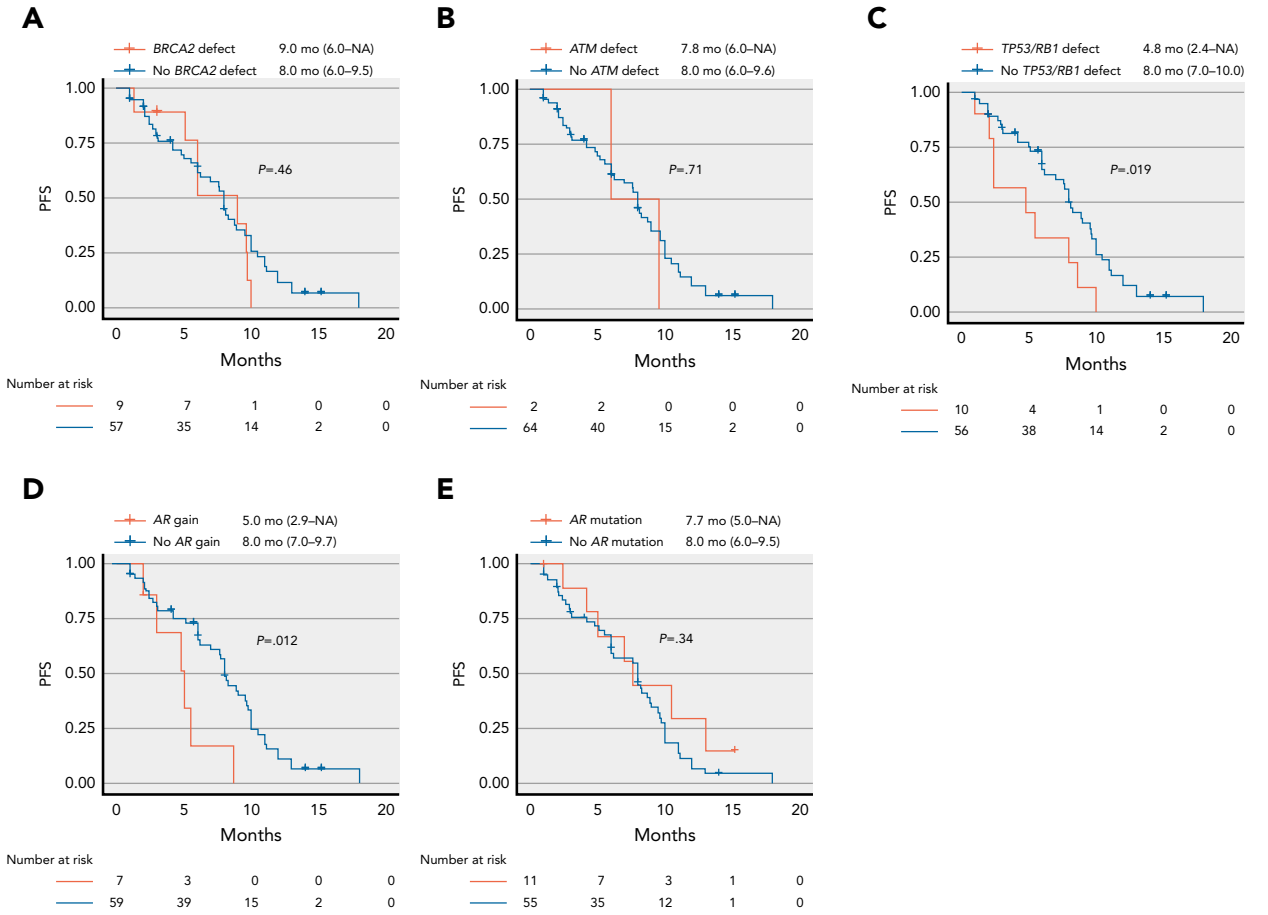
eFigure 3. Comparison of the alteration frequency of the selected DDR genes between the SU2C-PCF and the present cohorts.
Abbreviations: DDR, DNA damage repair; SU2C-PCF, Stand Up to Cancer–Prostate Cancer Foundation.



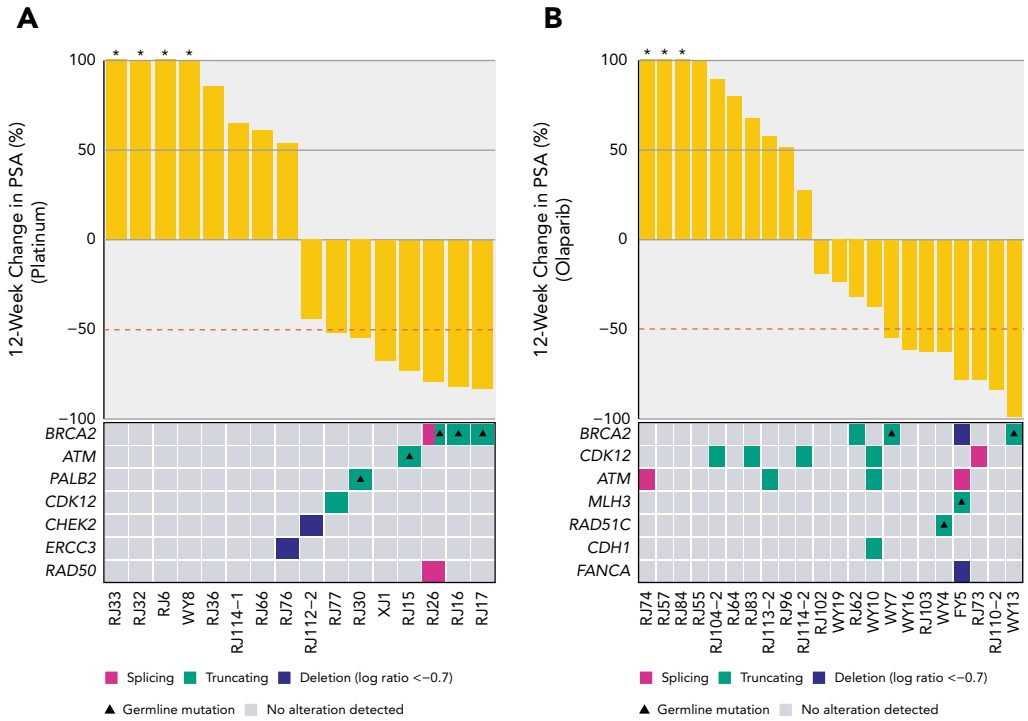
eFigure 4. Somatic profile of 14 patients with mCRPC from 2 serial ctDNA samples.
Abbreviations: ctDNA, circulating tumor DNA; mCRPC, metastatic castration-resistant prostate cancer.



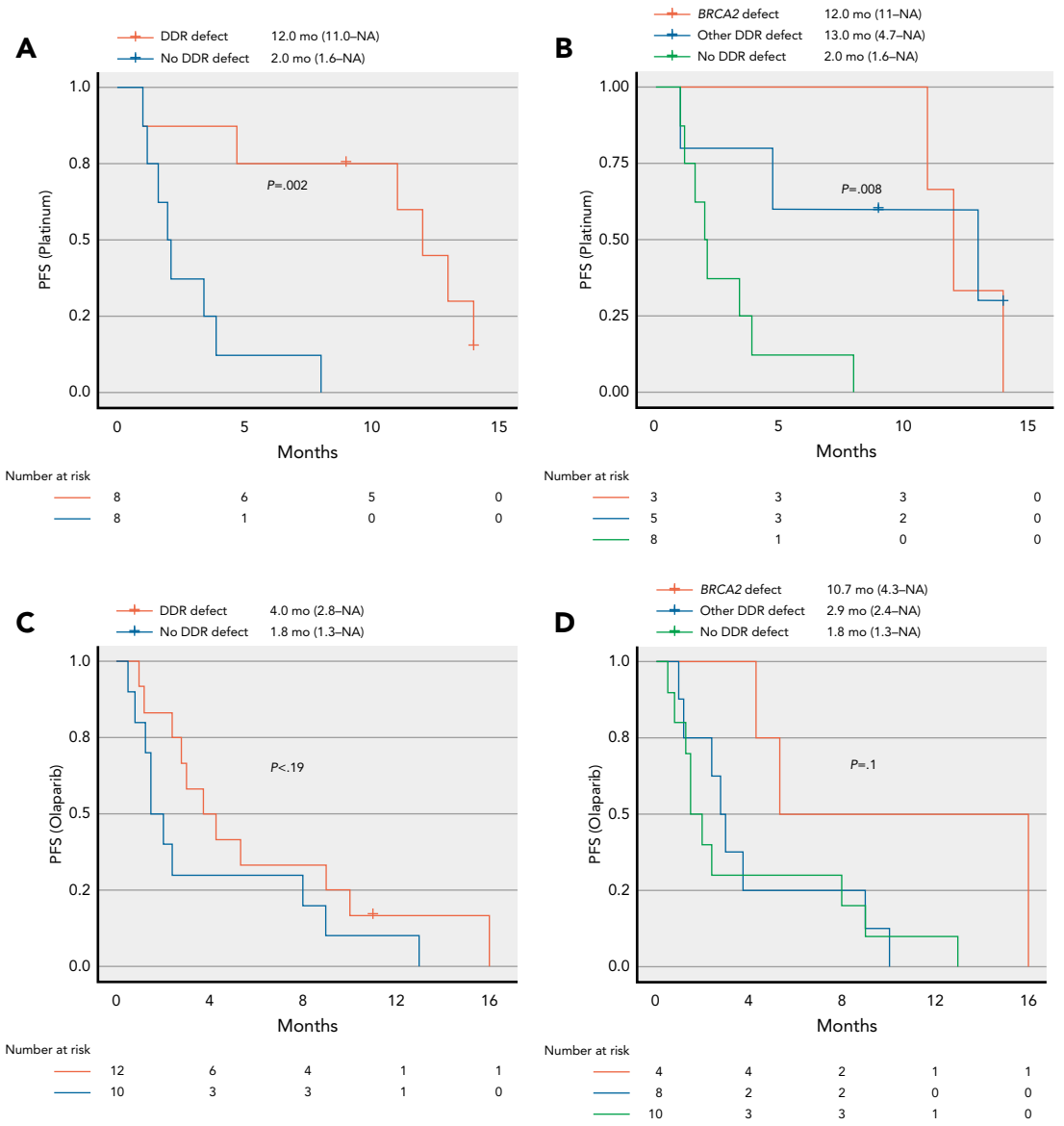
eFigure 5. Association between genomic alterations and clinical outcomes of abiraterone. Kaplan-Meier curves for PFS of patients with and without (A) a *BRCA2* defect, (B) an *ATM* defect, (C) a *TP53* or *RB1* defect, (D) *AR* gain, and (E) an *AR* mutation.
Abbreviations: NA, not available; PFS, progression-free survival.



eFigure 6. Association between genomic alterations and clinical outcomes of docetaxel. Kaplan-Meier curves for PFS of patients with and without (A) a *BRCA2* defect, (B) an *ATM* defect, (C) a *TP53* or *RB1* defect, (D) *AR* gain, and (E) an *AR* mutation.
Abbreviations: NA, not available; PFS, progression-free survival.



eFigure 7. Association between DDR gene defects and clinical outcomes of platinum-based chemotherapy and olaparib. (A) Waterfall plot for percentage of PSA change in response to platinum-based chemotherapy over 12 weeks. (B) Waterfall plot for percentage of PSA change in response to olaparib over 12 weeks. The asterisk (*) above each bar indicates that it was truncated.
Abbreviations: DDR, DNA damage repair; PSA, prostate-specific antigen.



eFigure 8. Association between DDR gene defects and clinical outcomes of platinum-based chemotherapy and olaparib. Kaplan-Meier curves for PFS of patients (A) with and without a DDR gene defect after platinum-based chemotherapy; (B) with a *BRCA2* defect, other DDR gene defects, and no DDR gene defect after platinum-based chemotherapy; (C) with and without a DDR gene defect after olaparib treatment; and (D) with a *BRCA2* defect, other DDR gene defects, and no DDR gene defect after olaparib treatment.
Abbreviations: DDR, DNA damage repair; NA, not available; PSA, prostate-specific antigen.

eTable 1. Treatment State Before Collection of 306 ctDNA Samples and 23 Tumor Tissues

Before ctDNA Sample Collection		Before Tumor Tissue Collection	
Patient ID	**Treatment for mCRPC Before Sequencing**	**Patient ID**	**Treatment for mCRPC Before Sequencing**
RJ1	Abiraterone	RJ38	Treatment-naïve
RJ2	Abiraterone	RJ101	Abiraterone
RJ3	Treatment-naïve	RJ104	Abiraterone
RJ4	Treatment-naïve	RJ111	Abiraterone
RJ5	Abiraterone and docetaxel	RJ112	Treatment-naïve
RJ6	Docetaxel	RJ113	Abiraterone and docetaxel
RJ7	Treatment-naïve	RJ114	Docetaxel, abiraterone, and platinum
RJ8	Docetaxel and abiraterone	RJ91	Abiraterone and docetaxel
RJ9	Treatment-naïve	RJ122	Abiraterone
RJ10	Treatment-naïve	RJ133	Abiraterone and docetaxel
RJ11	Abiraterone	RJ157	Treatment-naïve
RJ12-1	Treatment-naïve	RJ158	Docetaxel
RJ12-2	Docetaxel and abiraterone	SY3	Docetaxel and platinum
RJ13	Treatment-naïve	SY4	Docetaxel
RJ14	Treatment-naïve	SY5	Abiraterone and docetaxel
RJ15	Treatment-naïve	SY17	Treatment-naïve
RJ16	Treatment-naïve	SY18	Docetaxel, abiraterone, and olaparib
RJ17	Treatment-naïve	SY23	Docetaxel
RJ18	Treatment-naïve	SY26	Abiraterone
RJ19	Treatment-naïve	SY27	Docetaxel
RJ20	Treatment-naïve	SY28	Paclitaxel liposome
RJ21	Treatment-naïve	SY29	Treatment-naïve
RJ22-1	Treatment-naïve	SY30	Docetaxel and abiraterone
RJ22-2	Abiraterone		
RJ23-1	Treatment-naïve		
RJ23-2	Docetaxel		
RJ24	Abiraterone		
RJ25	Abiraterone		
RJ26	Treatment-naïve		
RJ27	Docetaxel		
RJ28	Treatment-naïve		
RJ29	Treatment-naïve		
RJ30	Docetaxel		
RJ31	Treatment-naïve		
RJ32	Abiraterone, enzalutamide, and docetaxel		
RJ33	Abiraterone and docetaxel		
RJ34	Abiraterone		
RJ35	Docetaxel and abiraterone		
RJ36	Abiraterone		
RJ37	Abiraterone		
RJ38	Treatment-naïve		
RJ39	Treatment-naïve		
RJ40	Docetaxel		

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eTable 1. Treatment State Before Collection of 306 ctDNA Samples and 23 Tumor Tissues (cont.)

Before ctDNA Sample Collection		Before Tumor Tissue Collection	
Patient ID	**Treatment for mCRPC Before Sequencing**	**Patient ID**	**Treatment for mCRPC Before Sequencing**
RJ41	Abiraterone		
RJ42	Treatment-naïve		
RJ43	Treatment-naïve		
RJ44	Treatment-naïve		
RJ45	Abiraterone and docetaxel		
RJ46	Abiraterone		
RJ47	Treatment-naïve		
RJ48	Treatment-naïve		
RJ49	Treatment-naïve		
RJ50	Treatment-naïve		
RJ51	Treatment-naïve		
RJ52	Abiraterone and docetaxel		
RJ53	Docetaxel		
RJ54	Treatment-naïve		
RJ55	Abiraterone		
RJ56	Treatment-naïve		
RJ57	Treatment-naïve		
RJ58	Abiraterone		
RJ59	Abiraterone		
RJ60	Treatment-naïve		
RJ61	Treatment-naïve		
RJ62	Abiraterone and docetaxel		
RJ63	Abiraterone and docetaxel		
RJ64	Abiraterone		
RJ65	Abiraterone		
RJ66	Treatment-naïve		
RJ67	Treatment-naïve		
RJ68	Abiraterone		
RJ69	Abiraterone		
RJ70	Abiraterone and docetaxel		
RJ71	Treatment-naïve		
RJ72	Abiraterone and docetaxel		
RJ73	Abiraterone		
RJ74	Treatment-naïve		
RJ75	Treatment-naïve		
RJ76	Docetaxel		
RJ77	Docetaxel		
RJ78	Abiraterone		
RJ79	Treatment-naïve		
RJ80	Treatment-naïve		
RJ81	Treatment-naïve		
RJ82	Treatment-naïve		
RJ83	Abiraterone		

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eTable 1. Treatment State Before Collection of 306 ctDNA Samples and 23 Tumor Tissues (cont.)

Before ctDNA Sample Collection		Before Tumor Tissue Collection	
Patient ID	**Treatment for mCRPC Before Sequencing**	**Patient ID**	**Treatment for mCRPC Before Sequencing**
RJ84	Abiraterone		
RJ85	Abiraterone		
RJ86	Treatment-naïve		
RJ87	Abiraterone		
RJ88	Abiraterone		
RJ89	Abiraterone		
RJ90	Treatment-naïve		
RJ91	Abiraterone and docetaxel		
RJ92	Treatment-naïve		
RJ93	Treatment-naïve		
RJ94	Treatment-naïve		
RJ95	Docetaxel		
RJ96	Abiraterone		
RJ97	Treatment-naïve		
RJ98	Treatment-naïve		
RJ99	Abiraterone and docetaxel		
RJ100	Abiraterone		
RJ101	Abiraterone		
RJ102	Abiraterone and enzalutamide		
RJ103	Abiraterone		
RJ104-1	Abiraterone		
RJ104-2	Abiraterone and olaparib		
RJ105-1	Abiraterone		
RJ105-2	Abiraterone and docetaxel		
RJ106-1	Treatment-naïve		
RJ106-2	Abiraterone and docetaxel		
RJ107-1	Treatment-naïve		
RJ107-2	Docetaxel		
RJ108-1	Treatment-naïve		
RJ108-2	Docetaxel		
RJ109-1	Treatment-naïve		
RJ109-2	Abiraterone and docetaxel		
RJ110-1	Treatment-naïve		
RJ110-2	Abiraterone and docetaxel		
RJ111-1	Abiraterone		
RJ111-2	Abiraterone and docetaxel		
RJ112-1	Treatment-naïve		
RJ112-2	Docetaxel		
RJ113-1	Treatment-naïve		
RJ113-2	Abiraterone and docetaxel		
RJ114-1	Docetaxel		
RJ114-2	Docetaxel and abiraterone		
RJ115	Abiraterone and enzalutamide		

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eTable 1. Treatment State Before Collection of 306 ctDNA Samples and 23 Tumor Tissues (cont.)

Before ctDNA Sample Collection		Before Tumor Tissue Collection	
Patient ID	**Treatment for mCRPC Before Sequencing**	**Patient ID**	**Treatment for mCRPC Before Sequencing**
RJ116	Docetaxel		
RJ117	Treatment-naïve		
RJ118	Treatment-naïve		
RJ119	Abiraterone and olaparib		
RJ120	Abiraterone		
RJ121	Treatment-naïve		
RJ122	Abiraterone		
RJ123	Abiraterone		
RJ124	Abiraterone		
RJ125	Treatment-naïve		
RJ126	Docetaxel		
RJ127	Abiraterone and docetaxel		
RJ128	Abiraterone and docetaxel		
RJ129	Docetaxel		
RJ130	Docetaxel		
RJ131	Docetaxel		
RJ132	Treatment-naïve		
RJ133	Abiraterone and docetaxel		
RJ134	Abiraterone		
RJ135	Docetaxel		
RJ136	Treatment-naïve		
RJ137	Abiraterone		
RJ138	Docetaxel and abiraterone		
RJ139	Abiraterone		
RJ140	Abiraterone		
RJ141	Abiraterone		
RJ142	Docetaxel and abiraterone		
RJ143	Docetaxel		
RJ144	Docetaxel		
RJ145	Treatment-naïve		
RJ146	Abiraterone		
RJ147	Abiraterone		
RJ148	Abiraterone		
RJ149	Abiraterone		
RJ150	Treatment-naïve		
RJ151	Treatment-naïve		
RJ152	Treatment-naïve		
RJ153	Docetaxel and abiraterone		
RJ154	Abiraterone		
RJ155	Abiraterone and olaparib		
RJ156	Abiraterone		
RJ157	Treatment-naïve		
RJ158	Docetaxel		

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eTable 1. Treatment State Before Collection of 306 ctDNA Samples and 23 Tumor Tissues (cont.)

Before ctDNA Sample Collection		Before Tumor Tissue Collection	
Patient ID	**Treatment for mCRPC Before Sequencing**	**Patient ID**	**Treatment for mCRPC Before Sequencing**
SY1	Abiraterone		
SY2	Abiraterone		
SY3	Docetaxel and platinum		
SY4	Docetaxel		
SY5	Abiraterone and docetaxel		
SY6	Treatment-naïve		
SY7	Docetaxel and abiraterone		
SY8	Docetaxel		
SY9	Abiraterone and enzalutamide		
SY10	Abiraterone and docetaxel		
SY11	Abiraterone and docetaxel		
SY12	Docetaxel, abiraterone, and enzalutamide		
SY13	Abiraterone, docetaxel, and platinum		
SY14	Abiraterone		
SY15	Abiraterone, docetaxel, and olaparib		
SY16	Docetaxel		
SY17	Treatment-naïve		
SY18	Docetaxel, abiraterone, and olaparib		
SY19	Treatment-naïve		
SY20	Treatment-naïve		
SY21	Treatment-naïve		
SY22	Docetaxel		
SY23	Docetaxel		
SY24	Treatment-naïve		
SY25	Treatment-naïve		
SY26	Abiraterone		
SY27	Docetaxel		
SY28	Paclitaxel liposome		
SY29	Treatment-naïve		
SY30	Docetaxel and abiraterone		
ZZ1	Abiraterone		
ZZ2	Abiraterone		
ZZ3	Radium-223 and abiraterone		
ZZ4	Abiraterone		
ZZ5	Docetaxel		
ZZ6	Abiraterone		
ZZ7	Abiraterone		
ZZ8	Docetaxel and abiraterone		
ZZ9	Abiraterone and docetaxel		
ZZ10	Abiraterone		
ZZ11	Abiraterone		
ZZ12	Docetaxel		
ZZ13	Abiraterone		

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eTable 1. Treatment State Before Collection of 306 ctDNA Samples and 23 Tumor Tissues (cont.)

Before ctDNA Sample Collection		Before Tumor Tissue Collection	
Patient ID	**Treatment for mCRPC Before Sequencing**	**Patient ID**	**Treatment for mCRPC Before Sequencing**
ZZ14	Docetaxel and abiraterone		
ZZ15	Abiraterone		
ZZ16	Docetaxel		
ZZ17	Abiraterone		
ZZ18	Treatment-naïve		
ZZ19	Docetaxel and abiraterone		
ZZ20	Docetaxel and abiraterone		
ZZ21	Abiraterone and docetaxel		
ZZ22	Abiraterone and docetaxel		
ZZ23	Abiraterone and enzalutamide		
ZZ24	Docetaxel and abiraterone		
ZZ25	Abiraterone		
ZZ26	Abiraterone		
ZZ27	Abiraterone		
ZZ28	Abiraterone		
ZZ29	Abiraterone		
WY1	Docetaxel and abiraterone		
WY2	Abiraterone		
WY3	Abiraterone and docetaxel		
WY4	Docetaxel		
WY5	Docetaxel and abiraterone		
WY6	Abiraterone and docetaxel		
WY7	Docetaxel		
WY8	Abiraterone and docetaxel		
WY9	Treatment-naïve		
WY10	Docetaxel and darolutamide		
WY11	Docetaxel and abiraterone		
WY12	Docetaxel and Abiraterone		
WY13	Abiraterone, docetaxel, and enzalutamide		
WY14	Abiraterone, enzalutamide, and docetaxel		
WY15	Abiraterone and docetaxel		
WY16	Abiraterone and docetaxel		
WY17	Abiraterone and docetaxel		
WY18	Abiraterone		
WY19	Abiraterone		
WY20	Treatment-naïve		
WY21	Abiraterone		
WY22	Abiraterone and docetaxel		
WY23	Docetaxel		
WY24	Docetaxel and abiraterone		
WY25	Docetaxel and abiraterone		
WY26	Docetaxel and abiraterone		
WY27	Treatment-naïve		

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eTable 1. Treatment State Before Collection of 306 ctDNA Samples and 23 Tumor Tissues (cont.)

Before ctDNA Sample Collection		Before Tumor Tissue Collection	
Patient ID	**Treatment for mCRPC Before Sequencing**	**Patient ID**	**Treatment for mCRPC Before Sequencing**
BYY1	Treatment-naïve		
BYY2	Abiraterone and docetaxel		
BYY3	Abiraterone		
BYY4	Abiraterone		
BYY5	Docetaxel		
BYY6	Abiraterone		
BYY7	Enzalutamide and abiraterone		
BYY8	Abiraterone		
BYY9	Abiraterone and enzalutamide		
BYY10	Treatment-naïve		
BYY11	Treatment-naïve		
BYY12	Abiraterone and docetaxel		
BYY13	Abiraterone		
BYY14	Abiraterone		
BYY15	Abiraterone		
BYY16	Abiraterone		
BYY17	Abiraterone		
BYY18	Abiraterone		
BYY19	Abiraterone		
BYY20	Docetaxel and abiraterone		
BYY21	Abiraterone		
BYY22	Abiraterone		
BYY23	Treatment-naïve		
BYY24	Abiraterone		
BYY25	Abiraterone		
BYY26	Abiraterone		
XJ1	Docetaxel		
XJ2	Treatment-naïve		
XJ3	Docetaxel		
XJ4	Docetaxel		
XJ5	Docetaxel and abiraterone		
XJ6	Abiraterone		
XJ7	Abiraterone and docetaxel		
XJ8	Docetaxel		
XJ9	Abiraterone		
FY1	Treatment-naïve		
FY2	Treatment-naïve		
FY3	Treatment-naïve		
FY4	Treatment-naïve		
FY5	Docetaxel and abiraterone		
FY6	Abiraterone		
FY7	Treatment-naïve		
ZR1	Treatment-naïve		

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eTable 1. Treatment State Before Collection of 306 ctDNA Samples and 23 Tumor Tissues (cont.)

Before ctDNA Sample Collection		Before Tumor Tissue Collection	
Patient ID	**Treatment for mCRPC Before Sequencing**	**Patient ID**	**Treatment for mCRPC Before Sequencing**
ZR2	Abiraterone and docetaxel		
ZR3	Abiraterone		
ZR4	Docetaxel and abiraterone		
ZR5	Abiraterone		
ZR6	Abiraterone and docetaxel		

Abbreviations: ctDNA, circulating tumor DNA; mCRPC, metastatic castration-resistant prostate cancer.

eTable 2. List of Common 50 Genes in 50-Gene, 66-Gene, 620-Gene, and 642-Gene Capture Panels	
AR	*CHEK2*
BARD1	*ERCC2*
BRIP1	*ERCC3*
CDH1	*ERCC4*
EPCAM	*ERCC5*
ESR1	*FANCA*
FAM175A	*FANCD2*
FOXA1	*HDAC2*
GEN1	*MLH1*
IDH1	*MLH3*
MUTYH	*MRE11A*
NBN	*MSH2*
NCOR1	*MSH6*
NCOR2	*PALB2*
PTEN	*PMS1*
SPOP	*PMS2*
STK11	*POLD1*
ZBTB16	*POLE*
RB1	*RAD51*
TP53	*RAD51B*
ATM	*RAD51C*
ATR	*XRCC4*
BRCA1	*RAD50*
BRCA2	*RAD51D*
CDK12	*HOXB13*

eTable 3. Clinical Characteristics of 306 ctDNA Samples From 292 Patients

Patient ID	Age at Baseline (y)	Gleason Score	PSA (ng/mL)	Time From ADT Initiation to mCRPC (mo)	cfDNA Yield (ng/mL plasma)	ctDNA (%)	Lymph Node Metastasis	Bone Metastases	Visceral Metastasis	Follow-Up (d)	Status at Last Follow-Up	Gene Panel Sequenced
RJ1	79	7	>152	54	48	33.6	Yes	Yes	No	1,093	Alive	50-gene
RJ2	72	8	22.2	7.7	14.8	32.7	Yes	Yes	No	933	Alive	50-gene
RJ3	66	7	6.4	13.7	16.5	30.8	Yes	Yes	No	933	Alive	50-gene
RJ4	59	8	215	11.6	8.5	5.7	Yes	Yes	No	1,115	Alive	50-gene
RJ5	74	8	96.2	10.8	14.9	0	Yes	Yes	No	1,133	Alive	50-gene
RJ6	71	8	52.3	10.8	9.8	0	Yes	Yes	No	1,115	Alive	50-gene
RJ7	74	7	46	28	70.2	22.8	Yes	Yes	No	1,121	Alive	50-gene
RJ8	71	7	17.7	102	27	2.4	Yes	Yes	No	779	Alive	50-gene
RJ9	68	7	68	35.5	9	0	Yes	Yes	No	699	Alive	50-gene
RJ10	69	7	7.8	86.1	8.3	3.7	Yes	Yes	No	1,072	Alive	50-gene
RJ11	74	9	564.8	55.4	17.3	4.9	Yes	Yes	No	699	Alive	50-gene
RJ12-1	60	9	12.4	52.4	6.5	0	Yes	Yes	No	941	Alive	50-gene
RJ12-2	61	9	Unknown	52.4	18.6	0	Yes	Yes	No	171	Alive	66-gene
RJ13	69	8	5	20.4	15.9	0	Yes	Yes	No	954	Alive	50-gene
RJ14	72	7	77.7	6.6	16.1	22.7	Yes	Yes	No	993	Alive	50-gene
RJ15	66	10	15.3	14.5	18.6	2.3	Yes	Yes	No	1,032	Alive	50-gene
RJ16	67	9	5.5	11.5	14.4	28.9	Yes	Yes	No	1,049	Alive	50-gene
RJ17	78	9	>154	9.9	13.5	0	Yes	Yes	No	1,032	Alive	50-gene
RJ18	76	7	>154	12.3	9.1	3.7	Yes	Yes	No	963	Alive	50-gene
RJ19	84	7	10.6	30	12	2.3	Yes	Yes	No	1,052	Alive	50-gene
RJ20	64	8	25.6	40.9	6	6	Yes	Yes	No	1,053	Alive	50-gene
RJ21	79	7	12.3	28	13.3	0	Yes	Yes	No	1,083	Alive	50-gene
RJ22-1	68	7	9.8	28	18.9	0	Yes	Yes	No	1,267	Alive	50-gene
RJ22-2	84	7	15.5	28	22.2	2.5	Yes	Yes	No	189	Alive	66-gene
RJ23-1	76	9	29.6	20.9	38.4	0	Yes	Yes	No	1,025	Alive	50-gene
RJ23-2	77	9	>158	20.9	42.9	48.8	Yes	Yes	No	284	Alive	66-gene
RJ24	70	8	107.4	8.3	4.8	2.4	Yes	Yes	No	1,102	Alive	50-gene
RJ25	68	9	126.9	17.1	130.5	64.8	Yes	Yes	No	1,004	Alive	50-gene
RJ26	67	9	10.9	14.1	4.1	6.5	Yes	Yes	No	1,034	Alive	50-gene
RJ27	62	8	>152	27	29.6	38.6	Yes	Yes	No	911	Alive	50-gene
RJ28	67	9	46	21.7	13.7	0	Yes	Yes	No	1,002	Alive	50-gene
RJ29	67	7	2,067.5	11.9	80.9	2.3	Yes	Yes	No	841	Alive	50-gene
RJ30	68	9	30	27.3	10.5	3.5	Yes	Yes	No	1,060	Alive	50-gene
RJ31	62	8	2,234	1.1	9.4	15.9	Yes	Yes	No	902	Alive	50-gene
RJ32	72	7	>154	30	13.8	15.5	Yes	Yes	No	705	Alive	50-gene
RJ33	66	6	>154	19	89.2	80.4	Yes	Yes	No	705	Alive	50-gene
RJ34	66	8	6.7	18	7.3	0	Yes	Yes	No	699	Alive	50-gene
RJ35	66	8	>100	23	6.8	0	Yes	Yes	No	673	Alive	50-gene
RJ36	78	8	220	16	8.1	0	Yes	Yes	No	671	Alive	50-gene
RJ37	68	9	11	16	10.5	32.6	Yes	Yes	No	671	Alive	50-gene
RJ38	54	NEPC	56	Unknown	160.8	73.7	Yes	Yes	No	659	Alive	50-gene

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eTable 3. Clinical Characteristics of 306 ctDNA Samples From 292 Patients (cont.)

Patient ID	Age at Baseline (y)	Gleason Score	PSA (ng/mL)	Time From ADT Initiation to mCRPC (mo)	cfDNA Yield (ng/mL plasma)	ctDNA (%)	Lymph Node Metastasis	Bone Metastases	Visceral Metastasis	Follow-Up (d)	Status at Last Follow-Up	Gene Panel Sequenced
RJ39	59	9	3.7	27	8.4	0	Yes	Yes	No	659	Alive	50-gene
RJ40	78	7	32.2	7	16.6	11.5	Yes	Yes	No	649	Alive	50-gene
RJ41	71	8	19.8	24	9	0	Yes	Yes	No	642	Alive	50-gene
RJ42	63	7	173	41	13.4	35.3	Yes	Yes	No	613	Alive	50-gene
RJ43	76	7	12.2	84	10.9	0	Yes	Yes	No	596	Alive	50-gene
RJ44	77	8	1,132	108	50.2	39	Yes	No	Yes	596	Alive	50-gene
RJ45	72	9	>154	24	8.2	8.5	Yes	Yes	No	593	Alive	50-gene
RJ46	69	7	42.9	20	3.3	1.4	Yes	Yes	No	589	Alive	50-gene
RJ47	84	8	456	18	14.1	1.9	Yes	Yes	No	586	Alive	50-gene
RJ48	80	6	17.5	96	10.8	3.8	Yes	Yes	No	579	Alive	50-gene
RJ49	70	7	34.6	41	14.1	0	Yes	Yes	No	568	Alive	50-gene
RJ50	66	9	42.5	28	10	0	Yes	Yes	No	564	Alive	50-gene
RJ51	68	9	77	36	10.7	28.5	Yes	Yes	No	558	Alive	50-gene
RJ52	72	9	27	16	11	1.8	Yes	Yes	No	719	Alive	50-gene
RJ53	71	NEPC	0.7	96	36.3	31.3	Yes	No	Yes	533	Alive	50-gene
RJ54	71	9	12.3	22	12.4	0	Yes	Yes	No	511	Alive	50-gene
RJ55	70	8	46	50	15.8	6.7	Yes	Yes	No	509	Alive	50-gene
RJ56	69	7	34.5	48	11.4	0	Yes	Yes	No	509	Alive	50-gene
RJ57	74	8	6.8	120	12.4	0	Yes	Yes	No	509	Alive	50-gene
RJ58	55	9	5.9	9	7.7	0	Yes	Yes	No	502	Alive	50-gene
RJ59	80	7	13.4	12	8.7	0	Yes	Yes	No	498	Alive	50-gene
RJ60	65	NEPC	2.2	Unknown	1,060	0	Yes	Yes	Yes	725	Alive	620-gene
RJ61	68	NEPC	1.9	Unknown	57.4	0	Yes	Yes	Yes	558	Alive	620-gene
RJ62	68	8	47.9	60	16	9.8	Yes	Yes	No	756	Alive	620-gene
RJ63	76	7	110	40	26.1	22.3	Yes	Yes	No	551	Alive	620-gene
RJ64	66	8	11.9	18	38	0	Yes	Yes	No	532	Alive	620-gene
RJ65	83	7	1231	48	47	55.6	Yes	Yes	No	381	Alive	620-gene
RJ66	61	9	16.7	10	5.8	1.7	Yes	Yes	No	367	Alive	620-gene
RJ67	64	8	18.4	19	11.1	0	Yes	Yes	No	366	Alive	620-gene
RJ68	74	8	32	19	11.7	13.4	Yes	Yes	No	428	Alive	620-gene
RJ69	80	8	34.6	26	41.8	0	Yes	Yes	No	484	Alive	66-gene
RJ70	70	7	327	20	485.8	66.3	Yes	Yes	No	480	Alive	66-gene
RJ71	71	7	13.8	24	10.8	5.7	Yes	Yes	No	479	Alive	66-gene
RJ72	78	8	52.3	32	1.1	3	Yes	Yes	No	469	Alive	66-gene
RJ73	68	8	571.4	17	19.3	52.7	Yes	Yes	No	462	Alive	66-gene
RJ74	67	7	313.9	36	105.6	59.5	Yes	Yes	No	459	Alive	66-gene
RJ75	65	8	17.8	23	15	1	Yes	Yes	No	459	Alive	66-gene
RJ76	83	10	372	20	11.4	50.4	Yes	Yes	No	458	Alive	66-gene
RJ77	59	9	278	29	11.5	7.2	Yes	Yes	No	449	Alive	66-gene
RJ78	72	8	32.7	20	6.2	0	Yes	Yes	No	449	Alive	66-gene
RJ79	73	7	22.6	20	8.3	2.4	Yes	Yes	No	438	Alive	66-gene

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eTable 3. Clinical Characteristics of 306 ctDNA Samples From 292 Patients (cont.)

Patient ID	Age at Baseline (y)	Gleason Score	PSA (ng/mL)	Time From ADT Initiation to mCRPC (mo)	cfDNA Yield (ng/mL plasma)	ctDNA (%)	Lymph Node Metastasis	Bone Metastases	Visceral Metastasis	Follow-Up (d)	Status at Last Follow-Up	Gene Panel Sequenced
RJ80	63	8	19.5	18	13.8	7.1	Yes	No	No	428	Alive	66-gene
RJ81	73	8	33.8	19	124.6	5.2	Yes	Yes	No	154	Dead	66-gene
RJ82	72	7	12.6	24	27.9	2.1	Yes	Yes	No	428	Alive	66-gene
RJ83	70	9	563.2	14	234	65.7	Yes	Yes	No	425	Alive	66-gene
RJ84	82	8	4.5	36	20	0	Yes	Yes	No	413	Alive	66-gene
RJ85	63	9	243.2	8	31	35.4	Yes	Yes	No	413	Alive	66-gene
RJ86	63	8	72.8	Unknown	18.6	32.6	Yes	Yes	No	413	Alive	66-gene
RJ87	78	10	158	10	33.8	25.9	Yes	Yes	No	406	Alive	66-gene
RJ88	65	8	277.2	48	71.5	35.5	Yes	Yes	No	406	Alive	66-gene
RJ89	55	8	43	19	8.7	3.8	Yes	Yes	No	400	Alive	66-gene
RJ90	58	10	236	24	9.2	0	Yes	Yes	No	397	Alive	66-gene
RJ91	55	9	352.7	16	13.8	59.1	Yes	Yes	No	397	Alive	66-gene
RJ92	62	7	45.2	12	960	3.8	Yes	Yes	No	60	Dead	66-gene
RJ93	68	8	3.2	60	13.4	0	Yes	Yes	No	386	Alive	66-gene
RJ94	86	8	1,234	40	18.7	43.7	Yes	Yes	No	383	Alive	66-gene
RJ95	73	8	10.8	22	8.1	2.9	Yes	Yes	No	378	Alive	66-gene
RJ96	83	8	29.8	36	12.5	0	Yes	Yes	No	375	Alive	66-gene
RJ97	70	8	4.9	30	10.1	1.7	Yes	No	No	372	Alive	66-gene
RJ98	80	7	9.7	22	10.3	0	Yes	Yes	No	370	Alive	66-gene
RJ99	62	9	233.2	16	113	27.8	Yes	Yes	No	418	Alive	66-gene
RJ100	76	9	32	15	5.3	0	Yes	No	No	431	Alive	66-gene
RJ101	63	9	8.9	9	29.7	70.9	Yes	No	No	470	Alive	66-gene
RJ102	74	8	>154	108	23	31	Yes	Yes	No	596	Alive	50-gene
RJ103	74	8	22.3	48	18.1	0	Yes	Yes	No	747	Alive	620-gene
RJ104-1	71	9	124.5	24	5	15.9	Yes	Yes	No	466	Alive	66-gene
RJ104-2	71	9	75.8	24	4.3	7.8	Yes	Yes	Yes	399	Alive	66-gene
RJ105-1	67	8	4.4	38.6	11.1	3.5	Yes	Yes	No	837	Alive	50-gene
RJ105-2	67	8	4.4	38.6	39.2	50.2	Yes	Yes	No	705	Alive	50-gene
RJ106-1	55	7	36.5	9.9	5.9	3	Yes	Yes	No	1,052	Alive	50-gene
RJ106-2	55	7	36.5	9.9	7.7	2.4	Yes	Yes	No	656	Alive	50-gene
RJ107-1	80	8	13	19.1	7.8	10.2	Yes	Yes	No	1,034	Alive	50-gene
RJ107-2	80	8	32.2	19.1	8.4	0	Yes	Yes	No	498	Alive	620-gene
RJ108-1	75	7	226.6	38.6	7.8	18.8	Yes	Yes	No	1,052	Alive	50-gene
RJ108-2	75	7	65.9	38.6	23.9	38.2	Yes	Yes	No	488	Alive	620-gene
RJ109-1	70	9	43.8	13	6.5	17.5	Yes	Yes	No	699	Alive	50-gene
RJ109-2	70	9	16.9	5	16	6.6	Yes	Yes	No	528	Alive	50-gene
RJ110-1	68	7	26	16	41	13.9	Yes	Yes	No	697	Alive	50-gene
RJ110-2	68	7	137.1	16	9.4	2	Yes	Yes	No	372	Alive	50-gene
RJ111-1	71	8	394.7	11	10	23	Yes	Yes	No	699	Alive	50-gene
RJ111-2	71	8	1,256	11	114.3	80.9	Yes	Yes	No	537	Alive	620-gene
RJ112-1	67	9	3.6	25.8	6.5	6.8	Yes	Yes	No	699	Alive	50-gene

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eTable 3. Clinical Characteristics of 306 ctDNA Samples From 292 Patients (cont.)

Patient ID	Age at Baseline (y)	Gleason Score	PSA (ng/mL)	Time From ADT Initiation to mCRPC (mo)	cfDNA Yield (ng/mL plasma)	ctDNA (%)	Lymph Node Metastasis	Bone Metastases	Visceral Metastasis	Follow-Up (d)	Status at Last Follow-Up	Gene Panel Sequenced
RJ112-2	67	9	6.3	25.8	14.5	3.5	Yes	Yes	No	428	Alive	66-gene
RJ113-1	67	8	26	10	15.2	4.2	Yes	Yes	No	719	Alive	50-gene
RJ113-2	67	8	120	10	14.3	10.9	Yes	Yes	No	470	Alive	66-gene
RJ114-1	47	9	20.4	12	8.8	0	Yes	Yes	No	523	Alive	50-gene
RJ114-2	47	9	131	12	12.6	12.1	Yes	Yes	No	377	Alive	66-gene
RJ115	74	8	49	36	15.5	51.9	Yes	Yes	No	719	Alive	50-gene
RJ116	60	9	20	15	11.4	0	Yes	Yes	No	365	Alive	66-gene
RJ117	70	7	1.2	84	11.3	1.6	Yes	No	No	320	Alive	66-gene
RJ118	76	8	>100	12	1,590	83	Yes	Yes	No	119	Dead	66-gene
RJ119	44	9	2.6	12	9.2	3.2	Yes	No	No	294	Alive	66-gene
RJ120	68	Unknown	>1,000	18	144	31.9	Yes	Yes	No	126	Dead	66-gene
RJ121	83	8	50	23	14.1	2.1	Yes	Yes	No	274	Alive	66-gene
RJ122	72	9	>100	18	44.4	49.9	Yes	Yes	No	89	Dead	66-gene
RJ123	89	Unknown	98	16	36.8	78.1	Yes	Yes	No	83	Dead	66-gene
RJ124	70	Unknown	>100	24	144	33.6	Yes	Yes	No	264	Alive	66-gene
RJ125	66	8	4	28	11.9	0	Yes	No	No	253	Alive	66-gene
RJ126	73	8	2.8	18	15	0	Yes	No	No	311	Alive	66-gene
RJ127	66	8	52.7	18	28.6	0	Yes	No	No	302	Alive	66-gene
RJ128	55	8	552	8	9.6	0	Yes	Yes	No	297	Alive	66-gene
RJ129	60	Unknown	99.4	24	19.1	4	Yes	Yes	No	255	Alive	66-gene
RJ130	74	7	6.7	45	21.6	1.5	Yes	Yes	No	255	Alive	66-gene
RJ131	75	7	17.6	36	49.8	82.7	Yes	Yes	No	287	Alive	66-gene
RJ132	78	8	53	36	11.3	0	Yes	Yes	No	285	Alive	66-gene
RJ133	67	9	160	24	266.9	71.5	Yes	Yes	Yes	110	Dead	66-gene
RJ134	69	7	17.1	28	10.7	3.8	Yes	Yes	No	355	Alive	66-gene
RJ135	71	10	38	19	9.7	56.5	Yes	Yes	No	346	Alive	66-gene
RJ136	79	9	20	30	27.8	0	Yes	Yes	No	249	Alive	66-gene
RJ137	82	Unknown	43	16	63.5	5.2	Yes	Yes	No	249	Alive	66-gene
RJ138	78	8	145	8	26.9	38.5	Yes	Yes	No	241	Alive	66-gene
RJ139	86	8	180	18	410	57.7	Yes	Yes	No	238	Alive	66-gene
RJ140	66	9	2	13	11.1	2.2	Yes	No	No	225	Alive	66-gene
RJ141	73	7	>100	168	23.4	42.1	Yes	Yes	No	221	Alive	66-gene
RJ142	66	9	1.6	25	19.1	0	Yes	No	No	220	Alive	66-gene
RJ143	63	10	50.7	8	92.6	76.3	Yes	Yes	No	215	Alive	642-gene
RJ144	60	9	3.6	20	10.3	1.1	Yes	Yes	No	210	Alive	66-gene
RJ145	69	9	41.5	26	12.8	2.5	Yes	Yes	No	204	Alive	642-gene
RJ146	78	Unknown	60	10	55	0	Yes	Yes	No	201	Alive	642-gene
RJ147	71	8	4.1	48	60.3	0	Yes	No	No	201	Alive	66-gene
RJ148	75	8	0.9	12	14	0	Yes	No	No	188	Alive	66-gene
RJ149	91	Unknown	40	60	19.2	2.8	Yes	Yes	No	185	Alive	642-gene
RJ150	75	Unknown	41.5	24	12.3	34.4	Yes	Yes	No	178	Alive	66-gene

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eTable 3. Clinical Characteristics of 306 ctDNA Samples From 292 Patients (cont.)

Patient ID	Age at Baseline (y)	Gleason Score	PSA (ng/mL)	Time From ADT Initiation to mCRPC (mo)	cfDNA Yield (ng/mL plasma)	ctDNA (%)	Lymph Node Metastasis	Bone Metastases	Visceral Metastasis	Follow-Up (d)	Status at Last Follow-Up	Gene Panel Sequenced
RJ151	66	10	15	18	18.6	0	Yes	Yes	No	173	Alive	66-gene
RJ152	64	9	3.7	18	29.5	27.4	Yes	Yes	No	172	Alive	66-gene
RJ153	61	8	>100	20	29.8	19.1	Yes	Yes	No	172	Alive	642-gene
RJ154	61	9	32	30	14.8	0	Yes	Yes	No	172	Alive	642-gene
RJ155	82	10	36	22	23.9	0	Yes	Yes	Yes	166	Alive	642-gene
RJ156	69	9	Unknown	18	12.8	0	Yes	No	No	161	Alive	642-gene
RJ157	81	9	8.8	6	19.3	71.6	Yes	No	No	680	Alive	66-gene
RJ158	68	NEPC	Unknown	10	12.5	29.5	Yes	Yes	Yes	90	Dead	66-gene
SY1	80	7	1.3	3	8.2	0	Yes	Yes	No	449	Alive	66-gene
SY2	64	8	35.2	5	5.9	0	Yes	Yes	No	434	Alive	66-gene
SY3	50	9	0.2	17	23.2	0	Yes	Yes	No	411	Alive	66-gene
SY4	59	10	0.8	Unknown	40.5	45.9	Yes	Yes	No	432	Alive	66-gene
SY5	72	9	11	7	5.3	2.2	Yes	Yes	No	418	Alive	642-gene
SY6	66	8	111.6	3	9.9	1.3	Yes	Yes	No	411	Alive	66-gene
SY7	64	8	172.6	4	29.6	63.7	Yes	Yes	No	722	Alive	620-gene
SY8	63	9	15.7	7.6	7.8	1.4	Yes	Yes	Yes	614	Alive	50-gene
SY9	78	7	68.8	15	8.3	6.2	Yes	No	No	554	Alive	620-gene
SY10	79	7	5.7	16	7	16.1	Yes	Yes	No	449	Alive	620-gene
SY11	65	7	42.8	Unknown	30.6	1.5	Yes	No	No	418	Alive	620-gene
SY12	56	Unknown	3.4	3	36.4	1.2	Yes	Yes	No	410	Alive	620-gene
SY13	52	9	122.6	20	136	0	Yes	Yes	Yes	367	Alive	620-gene
SY14	69	Unknown	Unknown	Unknown	16.4	0	Yes	Yes	No	406	Alive	620-gene
SY15	60	8	587	11	11.2	0	Unknown	Yes	No	298	Alive	620-gene
SY16	82	8	98	49	8.2	0	Unknown	Yes	No	285	Alive	66-gene
SY17	66	9	2.3	15	14	0	Yes	No	No	257	Alive	642-gene
SY18	78	9	7.8	10	33	16.4	Unknown	Yes	Yes	221	Alive	642-gene
SY19	68	9	3.9	12	13.4	1.4	Yes	Yes	No	208	Alive	642-gene
SY20	57	9	0.2	17	39	44.8	Yes	Yes	No	188	Alive	642-gene
SY21	63	10	3.4	25	20.6	0	Yes	Yes	No	187	Alive	642-gene
SY22	73	10	10.1	6	24.8	0	Yes	Yes	No	187	Alive	642-gene
SY23	69	6	15.4	21	16.7	16.8	Yes	No	Yes	180	Alive	642-gene
SY24	71	7	0.5	34	18.7	0	Yes	Yes	No	158	Alive	642-gene
SY25	68	Unknown	0	28	23.8	0	Unknown	Yes	No	157	Alive	642-gene
SY26	58	7	0.741	36	37.3	55.9	Yes	Yes	Yes	104	Alive	642-gene
SY27	54	Unknown	0.731	Unknown	9.2	0	Yes	Yes	No	75	Alive	642-gene
SY28	63	7	0.082	Unknown	12.1	33.5	Yes	Yes	Yes	69	Alive	642-gene
SY29	69	Unknown	36.44	Unknown	19.2	12.4	Yes	Yes	No	63	Alive	642-gene
SY30	59	8	0.819	Unknown	7.4	2	Yes	Yes	No	59	Alive	642-gene
ZZ1	71	8	724.2	15	12.5	1.6	No	Yes	No	390	Alive	66-gene
ZZ2	78	Unknown	21.7	Unknown	13.6	14.8	No	Yes	No	385	Alive	66-gene
ZZ3	67	Unknown	0.2	Unknown	13	0	No	Yes	No	375	Alive	66-gene

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eTable 3. Clinical Characteristics of 306 ctDNA Samples From 292 Patients (cont.)

Patient ID	Age at Baseline (y)	Gleason Score	PSA (ng/mL)	Time From ADT Initiation to mCRPC (mo)	cfDNA Yield (ng/mL plasma)	ctDNA (%)	Lymph Node Metastasis	Bone Metastases	Visceral Metastasis	Follow-Up (d)	Status at Last Follow-Up	Gene Panel Sequenced
ZZ4	78	10	45.2	Unknown	13.4	8.7	No	Yes	No	375	Alive	66-gene
ZZ5	60	9	17	Unknown	14.6	1.4	Yes	Yes	No	371	Alive	66-gene
ZZ6	80	9	20	11.5	8.6	44.3	No	Yes	No	371	Alive	66-gene
ZZ7	73	Unknown	11.3	Unknown	11.1	11.9	Yes	No	No	371	Alive	66-gene
ZZ8	60	9	592.2	25	12.1	9.9	No	Yes	No	371	Alive	66-gene
ZZ9	76	Unknown	2,175	20	44.2	23.8	No	Yes	No	369	Alive	66-gene
ZZ10	68	7	0	24	11.1	0	No	Yes	No	369	Alive	66-gene
ZZ11	69	8	135.7	6	22.8	2.6	No	Yes	No	369	Alive	66-gene
ZZ12	66	7	8.1	4	16.1	0	No	Yes	No	362	Alive	66-gene
ZZ13	78	8	108.4	12	10.8	1.7	No	Yes	No	362	Alive	66-gene
ZZ14	66	9	24.2	Unknown	21.1	7.4	Yes	Yes	No	356	Alive	66-gene
ZZ15	67	Unknown	16.4	Unknown	16	0	No	Yes	No	356	Alive	66-gene
ZZ16	75	8	0.4	7	7.6	0	Yes	Yes	No	356	Alive	66-gene
ZZ17	82	Unknown	13.1	Unknown	15.3	0	Yes	Yes	No	411	Alive	66-gene
ZZ18	62	10	10.1	7	22.4	11.2	No	Yes	No	356	Alive	66-gene
ZZ19	74	9	225	8	76.5	49.6	No	Yes	No	343	Alive	66-gene
ZZ20	75	6	557.6	13	14.7	19.3	No	Yes	No	322	Alive	66-gene
ZZ21	78	8	90	42	145	75.7	Yes	No	No	320	Alive	66-gene
ZZ22	68	8	427.2	94	32.2	15.2	No	Yes	No	314	Alive	66-gene
ZZ23	75	6	Unknown	28	12.3	2.2	No	Yes	No	277	Alive	66-gene
ZZ24	54	8	301.3	6	55	11.4	Yes	Yes	No	271	Alive	66-gene
ZZ25	81	9	25.3	9	18.7	21.6	No	Yes	No	257	Alive	66-gene
ZZ26	78	8	33.2	10	10.6	1.7	No	Yes	No	238	Alive	66-gene
ZZ27	63	9	8.4	27	10.8	1.6	Yes	Yes	No	193	Alive	66-gene
ZZ28	78	9	28	36	27.7	0	No	Yes	No	186	Alive	66-gene
ZZ29	72	6	3.3	9	11	0	Yes	Yes	No	161	Alive	66-gene
WY1	71	10	114.6	10	50.6	0	Yes	Yes	Yes	432	Alive	620-gene
WY2	63	10	334.1	18	110	12.5	Yes	Yes	Yes	30	Dead	66-gene
WY3	60	9	Unknown	Unknown	226	40.3	Yes	Yes	No	396	Alive	620-gene
WY4	50	9	466.7	9	440	81.9	Yes	Yes	Yes	391	Alive	620-gene
WY5	81	Unknown	404.3	8	24.6	20.2	Yes	Yes	No	391	Alive	620-gene
WY6	59	9	589.4	4	43.2	38.8	Yes	Yes	No	96	Dead	620-gene
WY7	60	9	87.9	17	9.3	10.2	Yes	Yes	No	392	Alive	620-gene
WY8	70	10	370.2	7	14.2	0	Yes	Yes	No	383	Alive	620-gene
WY9	70	NEPC	9.7	Unknown	12.5	0	Yes	No	No	377	Alive	620-gene
WY10	65	10	28.8	Unknown	27.2	40.9	Yes	Yes	No	376	Alive	620-gene
WY11	70	10	1	Unknown	12.7	0	Yes	Yes	No	371	Alive	620-gene
WY12	64	10	20.6	46	82	49.7	Yes	No	No	371	Alive	620-gene
WY13	67	10	73.9	6	26.8	30.2	Yes	Yes	Yes	509	Alive	620-gene
WY14	52	9	Unknown	8	35.9	3.7	Yes	Yes	No	538	Dead	50-gene
WY15	77	9	20.9	8	20.4	44.1	Yes	Yes	Yes	451	Alive	620-gene

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eTable 3. Clinical Characteristics of 306 ctDNA Samples From 292 Patients (cont.)

Patient ID	Age at Baseline (y)	Gleason Score	PSA (ng/mL)	Time From ADT Initiation to mCRPC (mo)	cfDNA Yield (ng/mL plasma)	ctDNA (%)	Lymph Node Metastasis	Bone Metastases	Visceral Metastasis	Follow-Up (d)	Status at Last Follow-Up	Gene Panel Sequenced
WY16	84	10	698.4	36	59.6	23.7	Yes	Yes	No	445	Alive	620-gene
WY17	76	10	26.47	Unknown	22.8	0	Yes	Yes	No	438	Alive	620-gene
WY18	80	8	>1,000	Unknown	69.4	16.7	Yes	Yes	No	432	Alive	620-gene
WY19	74	10	482	12	18	37.4	Yes	Yes	No	424	Alive	620-gene
WY20	68	8	3.27	7	13.6	3.4	Yes	Yes	No	349	Alive	620-gene
WY21	74	9	21.5	11	199	49.1	Yes	Yes	No	333	Alive	620-gene
WY22	77	9	22.4	6	49.2	0	Yes	Yes	No	322	Alive	620-gene
WY23	65	10	46.1	Unknown	22.6	10.6	Yes	Yes	No	304	Alive	620-gene
WY24	75	Unknown	86.7	13	19.6	41.3	Yes	Yes	No	279	Alive	642-gene
WY25	79	9	4.4	6	12.2	4.7	Yes	Yes	No	269	Alive	66-gene
WY26	71	10	124.3	8	22.6	5.6	Yes	Yes	No	205	Alive	642-gene
WY27	66	9	185.4	6	9.1	0	Yes	Yes	No	154	Alive	66-gene
BYY1	84	9	14.4	35.8	31.8	0	Yes	Yes	No	403	Alive	66-gene
BYY2	69	8	0	99.7	17	0	Yes	Yes	No	446	Alive	66-gene
BYY3	61	Unknown	286.8	17.4	14.7	27.6	Yes	Yes	No	446	Alive	66-gene
BYY4	81	8	363	48.7	14.3	10.6	Yes	Yes	No	439	Alive	66-gene
BYY5	64	6	28	95.4	23.2	58.4	Yes	Yes	No	438	Alive	66-gene
BYY6	85	9	95.2	49.6	8.2	0	Yes	Yes	No	459	Alive	66-gene
BYY7	65	8	12	6.8	4.2	0	Yes	Yes	No	468	Alive	66-gene
BYY8	76	7	10	11	19.5	24.1	Yes	Yes	No	440	Alive	66-gene
BYY9	77	9	174	21.8	84	52.6	Yes	Yes	Yes	37	Dead	66-gene
BYY10	70	Unknown	32.9	10.6	11.6	22.8	Yes	Yes	No	438	Alive	66-gene
BYY11	63	10	48.7	3.1	18.6	29	Yes	Yes	No	415	Alive	66-gene
BYY12	63	7	278	60.6	54.9	29.7	Yes	Yes	Yes	403	Alive	66-gene
BYY13	62	7	40.1	89.2	8.9	1.8	Yes	Yes	No	382	Alive	66-gene
BYY14	73	9	730	8	142	34.7	Yes	Yes	No	99	Dead	66-gene
BYY15	80	8	35.6	53.8	64.4	0	Yes	Yes	No	377	Alive	66-gene
BYY16	80	Unknown	66.8	31	23.9	30.3	Yes	Yes	No	349	Alive	66-gene
BYY17	79	9	41.3	38.6	14.5	9	No	Yes	No	349	Alive	66-gene
BYY18	65	9	2,467	16.9	22.8	50.9	Yes	Yes	No	335	Alive	66-gene
BYY19	68	Unknown	4.8	44.5	11.1	0	No	Yes	Yes	321	Alive	66-gene
BYY20	64	7	180.6	48.7	14.1	0	Yes	Yes	Yes	314	Alive	66-gene
BYY21	64	10	39	5.7	45.4	4.1	Yes	Yes	Yes	279	Alive	66-gene
BYY22	67	10	777.5	33	54.8	0	Yes	Yes	No	258	Alive	66-gene
BYY23	80	Unknown	32.1	53	7.1	0	Yes	Yes	No	239	Alive	66-gene
BYY24	83	7	2,738	16	358	50.2	Yes	Yes	Yes	16	Dead	66-gene
BYY25	64	9	822	24	251.1	0	Yes	Yes	Yes	28	Dead	66-gene
BYY26	71	9	11.5	26	11.6	31.5	No	Yes	No	161	Alive	66-gene
XJ1	63	9	4.2	10	15.1	0	Yes	Yes	No	600	Alive	50-gene
XJ2	68	9	198.3	6	13.5	63.3	Yes	Yes	No	563	Alive	50-gene
XJ3	67	7	14.3	24	5.6	18.7	Yes	Yes	No	550	Alive	50-gene

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eTable 3. Clinical Characteristics of 306 ctDNA Samples From 292 Patients (cont.)

Patient ID	Age at Baseline (y)	Gleason Score	PSA (ng/mL)	Time From ADT Initiation to mCRPC (mo)	cfDNA Yield (ng/mL plasma)	ctDNA (%)	Lymph Node Metastasis	Bone Metastases	Visceral Metastasis	Follow-Up (d)	Status at Last Follow-Up	Gene Panel Sequenced
XJ4	71	9	0	Unknown	10.5	0	No	No	Yes	550	Alive	50-gene
XJ5	71	8	20.3	7	15.3	0	Yes	Yes	Yes	543	Alive	50-gene
XJ6	69	7	940	15	282	51.9	Yes	Yes	No	375	Alive	66-gene
XJ7	62	Unknown	937.6	8	59.2	54.8	Unknown	Yes	No	357	Alive	66-gene
XJ8	67	9	20.8	8	55.6	1.6	No	Yes	No	314	Alive	66-gene
XJ9	64	Unknown	86.9	120	17.4	1.6	Yes	Yes	Yes	282	Alive	66-gene
FY1	80	Unknown	Unknown	Unknown	15.2	0	Yes	Yes	No	473	Alive	66-gene
FY2	75	Unknown	Unknown	Unknown	9.2	0	Yes	Yes	No	429	Alive	66-gene
FY3	69	7	151.3	Unknown	40.2	41	Yes	Yes	No	424	Alive	66-gene
FY4	79	Unknown	Unknown	Unknown	12.1	12.3	Yes	Yes	No	523	Alive	50-gene
FY5	76	Unknown	4,737	15	369.2	72	Yes	Yes	No	518	Alive	50-gene
FY6	69	Unknown	Unknown	Unknown	8.8	0	Yes	Yes	No	511	Alive	50-gene
FY7	79	Unknown	Unknown	Unknown	24.4	19.3	Yes	Yes	No	369	Alive	66-gene
ZR1	64	8	8.2	11	6.3	1.6	No	Yes	No	468	Alive	66-gene
ZR2	49	Unknown	>600	5	73.2	59.1	Yes	Yes	No	427	Alive	620-gene
ZR3	91	9	206	96	21	11.4	Yes	Yes	No	395	Alive	620-gene
ZR4	47	9	111.3	10	13.6	7.6	Yes	Yes	No	285	Alive	66-gene
ZR5	78	8	69.9	Unknown	45.6	57	Yes	Yes	No	281	Alive	642-gene
ZR6	68	9	0	4	367.2	75	Yes	Yes	No	265	Alive	642-gene

Abbreviations: cfDNA, circulating free DNA; ctDNA, circulating tumor DNA; mCRPC, metastatic castration-resistant prostate cancer; NEPC, neuroendocrine prostate cancer; PSA, prostate-specific antigen.

eTable 4. Somatic Mutations Detected in ctDNA and Matched Tumor Tissue of 23 Patients

Sample	Chrom	Position	Ref	Alt	Gene	Effect	Tumor Tissue AF (%)	ctDNA AF (%)
Mutations detected in both ctDNA and tumor tissue								
RJ101	chr14	38060784	A	G	*FOXA1*	Nonsynonymous SNV p.I402T	23.10%	29.10%
RJ101	chr14	38060785	T	A	*FOXA1*	Nonsynonymous SNV p.I402F	23.60%	29.40%
RJ101	chr17	37627561	—	A	*CDK12*	Frameshift insertion p.D494fs	41.20%	56.20%
RJ113-2	chr22	29095882	G	A	*CHEK2*	Nonsynonymous SNV p.R318C	11.60%	4.00%
RJ113-2	chr10	89717672	C	T	*PTEN*	Stopgain p.R233X	23.80%	5.00%
RJ114-2	chr14	38061218	GCCGTTCTCGAA CATGTTGCCGGAG	—	*FOXA1*	Frameshift deletion p.S250fs	55.60%	7.10%
RJ114-2	chr17	37619206	CTACGTAG	T	*CDK12*	Frameshift deletion p.Y295fs	30.30%	3.60%
RJ114-2	chr17	37627919	C	T	*CDK12*	Stopgain p.Q612X	29.80%	3.40%
RJ38	chr10	89720799	TA	CTTTAACAAAAAATGAT CTTACTTTAACAAAAAA TATCTTACTTTAACAAA AAATTTTTTTGTTTACTT AAAGTAAAATAT	*PTEN*	Nonframeshift insertion p.V317delinsAL	56.90%	35.00%
RJ38	chr13	48955572	G	A	*RB1*	Stopgain p.W563X	72.80%	60.80%
RJ104-1	chr14	38061191	G	T	*FOXA1*	Nonsynonymous SNV p.F266L	46.90%	3.90%
RJ104-1	chr17	37627619	—	T	*CDK12*	Frameshift insertion p.V513fs	49.20%	9.70%
RJ111-1	chr17	7577505	T	A	*TP53*	Nonsynonymous SNV p.D259V	51.10%	11.90%
RJ111-1	chr12	124810826	G	C	*NCOR2*	Nonsynonymous SNV p.P2425R	35.20%	13.70%
RJ112-1	chr17	37627793	C	T	*CDK12*	Stopgain p.Q570X	31.40%	3.80%
SY18	chr16	23641351	TAAAGGAGTA	—	*PALB2*	Frameshift deletion p.Y705fs	0.427	0.027
SY18	chr13	48919259	ACCAAAGT	—	*RB1*	Frameshift deletion p.T142fs	0.605	0.031
SY18	chr17	7578550	G	A	*TP53*	Nonsynonymous SNV p.S127F	0.889	0.1
SY18	chr14	38061226	CGAACATGTTGC	—	*FOXA1*	Nonframeshift deletion p.G251_F254del	0.472	0.086
RJ133	chr17	37618588	CTTCAAACTA GACCGAAGG	—	*CDK12*	Frameshift deletion p.F89fs	0.286	0.572
SY29	chr17	7577575	A	G	*TP53*	Nonsynonymous SNV p.Y236H	0.664	0.074
RJ158	chr13	49033917	A	C	*RB1*	Nonsynonymous SNV p.Q685P	0.25	0.186
RJ157	chr14	38061200	CTGGCGGCG	—	*FOXA1*	Nonframeshift deletion p.R261_Q263del	0.32	0.234
RJ157	chr11	108202285	G	C	*ATM*	Splicing	0.89	0.577
SY28	chr3	37081761	A	G	*MLH1*	Nonsynonymous SNV p.Y548C	0.448	0.219
SY28	chrX	66937372	G	T	*AR*	Nonsynonymous SNV p.W742C	0.467	0.229
SY26	chr2	209113113	G	A	*IDH1*	Nonsynonymous SNV p.R132C	0.609	0.354

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eTable 4. Somatic Mutations Detected in ctDNA and Matched Tumor Tissue of 23 Patients (cont.)

Sample	Chrom	Position	Ref	Alt	Gene	Effect	Tumor Tissue AF (%)	ctDNA AF (%)
SY26	chr7	6042213	C	G	*PMS2*	Nonsynonymous SNV p.M136I	0.261	0.127
SY26	chr17	7577147	AG	—	*TP53*	Frameshift deletion p.L264fs	0.911	0.406
SY30	chr17	37619280	—	A	*CDK12*	Stopgain p.Y319X	0.259	0.01
SY30	chr17	37657610	CT	AA	*CDK12*	Nonsynonymous SNV p.L843K	0.257	0.015
SY5	chr10	89711982	T	—	*PTEN*	Frameshift deletion p.F200fs	0.632	0.018
SY5	chr17	47696644	A	C	*SPOP*	Nonsynonymous SNV p.F102V	0.486	0.015
Mutations detected in tumor tissue but missed in ctDNA								
RJ113-2	chr13	48878126	—	C	*RB1*	Frameshift insertion p.P29fs	14.90%	
RJ114-2	chr16	23641352	A	—	*PALB2*	Stopgain p.L708X	7.70%	
SY30	chr14	38060682	—	T	*FOXA1*	Frameshift insertion p.S436fs	23.50%	
Mutations detected in ctDNA but missed in tumor tissue								
RJ114-2	chrX	66937372	G	C	*AR*	Nonsynonymous SNV p.W742C		1.50%
RJ114-2	chrX	66937371	G	T	*AR*	Nonsynonymous SNV p.W742L		5.10%
SY4	chr6	152265487	C	A	*ESR1*	Nonsynonymous SNV p.Q314K		22.00%
SY4	chr13	32945148	A	—	*BRCA2*	Frameshift deletion p.K2849fs		31.60%
RJ104-1	chr11	114113039	G	A	*ZBTB16*	Nonsynonymous SNV p.R535H		1.20%
RJ104-1	chrX	66937372	G	C	*AR*	Nonsynonymous SNV p.W742C		2.20%
RJ104-1	chrX	66943552	A	G	*AR*	Nonsynonymous SNV p.T878A		1.60%
RJ101	chrX	66937372	G	T	*AR*	Nonsynonymous SNV p.W742C		1.40%
RJ101	chrX	66765158	T	A	*AR*	Nonsynonymous SNV p.L57Q		9.50%
RJ112-1	chr3	142183998	G	T	*ATR*	Nonsynonymous SNV p.P2328T		1.90%
RJ112-1	chr2	47641507	C	A	*MSH2*	Nonsynonymous SNV p.Q298K		1.10%
RJ112-1	chr10	89720783	G	A	*PTEN*	Nonsynonymous SNV p.D312N		1.10%
RJ112-1	chrX	66905791	G	A	*AR*	Nonsynonymous SNV p.R542Q		1.30%
RJ112-1	chr13	32914782	C	T	*BRCA2*	Nonsynonymous SNV p.T2097M		1.80%
RJ112-1	chr16	14024643	—	GGGA	*ERCC4*	Frameshift insertion p.I290fs		1.20%
RJ113-2	chr11	108098542	G	T	*ATM*	Stopgain p.E38X		1.20%
RJ133	chrX	66943552	A	G	*AR*	Nonsynonymous SNV p.T878A		8.10%

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eTable 4. Somatic Mutations Detected in ctDNA and Matched Tumor Tissue of 23 Patients (cont.)

Sample	Chrom	Position	Ref	Alt	Gene	Effect	Tumor Tissue AF (%)	ctDNA AF (%)
RJ157	chr12	124819159	A	C	*NCOR2*	Nonsynonymous SNV p.V2139G		1.90%
SY28	chr17	7577548	C	T	*TP53*	Nonsynonymous SNV p.G245S		7.80%
RJ122	chrX	66931463	T	A	*AR*	Nonsynonymous SNV p.L702H		15.00%
RJ122	chr14	38061220	CGTTCT	—	*FOXA1*	Nonframeshift deletion p.E255_N256del		34.20%

Abbreviations: AF, allele fraction; Alt, alteration; Chrom, chromosome; ctDNA, circulating tumor DNA; Ref, reference.

eTable 5. All Filtered Somatic Mutations and Deleterious Germline Mutations Detected

Chromosome	Position	Ref	Alteration	Gene	Effect	Patient ID	Allele (%)	Alt DP
Somatic mutations								
chr1	45797111	T	G	*MUTYH*	Nonsynonymous SNV p.H435P	RJ108-2	19.70	567
chr1	45798458	G	A	*MUTYH*	Nonsynonymous SNV p.R185W	XJ2	8.70	495
chr1	45795060	C	T	*MUTYH*	Nonsynonymous SNV p.R523H	XJ2	6.30	293
chr1	45797118	C	T	*MUTYH*	Nonsynonymous SNV p.A433T	RJ77	3.00	165
chr1	45797111	T	G	*MUTYH*	Nonsynonymous SNV p.H435P	RJ108-1	1.40	157
chr2	17941286	A	T	*GEN1*	Nonsynonymous SNV p.T26S	RJ65	40.00	1,037
chr2	48032100	G	A	*MSH6*	Nonsynonymous SNV p.V1164M	RJ118	36.10	1,474
chr2	48028267	T	G	*MSH6*	Nonsynonymous SNV p.S1049A	BYY14	21.40	768
chr2	215593542	C	T	*BARD1*	Nonsynonymous SNV p.R731H	RJ27	18.80	1,638
chr2	48027350	—	G	*MSH6*	Frameshift insertion p.E744fs	RJ51	18.00	338
chr2	48030639	—	C	*MSH6*	Frameshift insertion p.F1088fs	ZZ6	17.60	107
chr2	215645439	A	G	*BARD1*	Nonsynonymous SNV p.F387L	RJ44	14.00	865
chr2	17941245	C	A	*GEN1*	Nonsynonymous SNV p.P12H	XJ2	7.90	336
chr2	209113113	G	A	*IDH1*	Nonsynonymous SNV p.R132C	WY2	7.40	235
chr2	209113113	G	A	*IDH1*	Nonsynonymous SNVp.R132C	SY26	35.40	908
chr2	17941352	G	A	*GEN1*	Nonsynonymous SNV p.V48I	XJ2	6.70	284
chr2	48025819	C	G	*MSH6*	Nonsynonymous SNV p.P233A	RJ62	5.40	76
chr2	17961920	C	G	*GEN1*	Nonsynonymous SNV p.P481A	ZZ20	3.10	37
chr2	47639601	T	G	*MSH2*	Nonsynonymous SNV p.F232V	RJ51	2.80	29
chr2	190732542	A	C	*PMS1*	Nonsynonymous SNV p.H787P	RJ65	2.50	34
chr2	17961295	A	G	*GEN1*	Nonsynonymous SNV p.I439V	RJ95	2.30	12
chr2	48033667	C	A	*MSH6*	Nonsynonymous SNV p.A1293D	RJ24	1.60	47
chr2	190732541	C	T	*PMS1*	Nonsynonymous SNV p.H787Y	RJ20	1.40	42
chr2	47641552	—	CTA	*MSH2*	Nonframeshift insertion p.F313delinsSI	RJ20	1.40	26
chr2	47705553	C	T	*MSH2*	Nonsynonymous SNV p.H785Y	RJ33	1.30	72
chr2	47600600	A	T	*EPCAM*	Splicing	FY3	1.10	10
chr2	47641507	C	A	*MSH2*	Nonsynonymous SNV p.Q298K	RJ112-1	1.10	36
chr2	48033667	C	A	*MSH6*	Nonsynonymous SNV p.A1293D	ZZ11	1.10	16
chr2	190660598	A	C	*PMS1*	Nonsynonymous SNV p.N79T	RJ20	1.00	42
chr2	47639575	T	A	*MSH2*	Nonsynonymous SNV p.L223Q	RJ20	1.00	23
chr2	47630424	A	T	*MSH2*	Nonsynonymous SNV p.T32S	ZR1	1.00	40
chr3	142281715	G	A	*ATR*	Stopgain p.R177X	XJ7	34.50	1,470
chr3	142218475	CCAAATA GTTTTCCA	—	*ATR*	Nonframeshift deletion p.V1787_L1791del	ZR6	23.50	603
chr3	142184006	A	C	*ATR*	Nonsynonymous SNV p.M2325R	BYY11	18.00	615
chr3	10127540	C	T	*FANCD2*	Nonsynonymous SNV p.A1090V	RJ108-2	16.50	342
chr3	142279186	A	G	*ATR*	Nonsynonymous SNV p.I487T	RJ153	11.70	226

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eTable 5. All Filtered Somatic Mutations and Deleterious Germline Mutations Detected (cont.)

Chromosome	Position	Ref	Alteration	Gene	Effect	Patient ID	Allele (%)	Alt DP
chr3	142180827	T	—	*ATR*	Frameshift deletion p.T2383fs	SY7	9.60	364
chr3	142180870	A	C	*ATR*	Nonsynonymous SNV p.I2368M	WY13	8.30	145
chr3	10089729	C	G	*FANCD2*	Nonsynonymous SNV p.C469W	WY23	6.40	127
chr3	142171980	A	C	*ATR*	Nonsynonymous SNV p.V2584G	BYY4	4.20	61
chr3	10089723	G	—	*FANCD2*	Frameshift deletion p.Y468fs	BYY21	2.50	87
chr3	142215203	C	G	*ATR*	Nonsynonymous SNV p.K1966N	RJ4	2.40	119
chr3	142183998	G	T	*ATR*	Nonsynonymous SNV p.P2328T	RJ112-1	1.90	49
chr3	142188309	G	T	*ATR*	Nonsynonymous SNV p.A2141D	RJ106-2	1.90	13
chr3	10114667	T	C	*FANCD2*	Splicing	RJ24	1.70	20
chr3	37055960	G	—	*MLH1*	Frameshift deletion p.A239fs	RJ71	1.50	14
chr3	37055962	CTT	—	*MLH1*	Nonframeshift deletion p.F240del	RJ71	1.50	14
chr3	37045901	A	G	*MLH1*	Nonsynonymous SNV p.S106G	BYY14	1.20	36
chr3	37045892	G	A	*MLH1*	Nonsynonymous SNV p.A103T	BYY14	1.20	34
chr3	37081761	A	G	*MLH1*	Nonsynonymous SNVp.Y548C	SY28	21.90	291
chr3	142242899	G	T	*ATR*	Nonsynonymous SNV p.A1363E	RJ115	1.20	27
chr3	10122811	—	AACAACTTGC AAATAGGCTTTAT ACAAGAATC	*FANCD2*	Stopgain p.S1002_H1003delinsX	ZZ2	1.20	35
chr3	10076451	—	TCATTTCATCC TTTCACTTCTTT CCCTTCCTCC GTC	*FANCD2*	Nonframeshift insertion p.S116delins FISSFHFFP FLRP	RJ26	1.10	16
chr3	142188929	T	—	*ATR*	Frameshift deletion p.A2107fs	RJ140	1.10	10
chr3	10127540	C	T	*FANCD2*	Nonsynonymous SNV p.A1090V	RJ108-1	1.00	79
chr3	142254042	—	AGATCGGAA GAGCACAC	*ATR*	Frameshift insertion p.S1276fs	RJ24	1.00	23
chr3	142266710	A	G	*ATR*	Nonsynonymous SNV p.F1072L	RJ18	1.00	72
chr5	131915013	G	C	*RAD50*	Nonsynonymous SNV p.G124R	RJ124	16.50	458
chr5	131940599	C	A	*RAD50*	Nonsynonymous SNV p.Q876K	XJ2	4.90	174
chr5	131927569	G	T	*RAD50*	Nonsynonymous SNV p.A546S	RJ110-2	1.40	22
chr5	131923615	G	T	*RAD50*	Splicing	RJ26	1.30	19
chr5	131915722	—	ATAG	*RAD50*	Frameshift insertion p.V241fs	RJ24	1.30	27
chr5	131930581	A	T	*RAD50*	Nonsynonymous SNV p.E605V	RJ20	1.10	38
chr5	82554396	G	A	*XRCC4*	Nonsynonymous SNV p.D265N	RJ20	1.00	36
chr6	152265487	C	A	*ESR1*	Nonsynonymous SNV p.Q314K	SY4	22.00	859
chr6	152382194	T	C	*ESR1*	Nonsynonymous SNV p.F435S	FY3	18.40	304
chr6	152129177	C	A	*ESR1*	Nonsynonymous SNV p.L44M	RJ51	13.20	497
chr6	114270400	A	C	*HDAC2*	Nonsynonymous SNV p.Y222D	FY7	11.40	565
chr6	152129323	C	A	*ESR1*	Nonsynonymous SNV p.N92K	RJ31	4.60	604

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eTable 5. All Filtered Somatic Mutations and Deleterious Germline Mutations Detected (cont.)

Chromosome	Position	Ref	Alteration	Gene	Effect	Patient ID	Allele (%)	Alt DP
chr6	152332868	G	A	*ESR1*	Nonsynonymous SNV p.V392I	ZZ11	1.50	43
chr6	114279847	A	C	*HDAC2*	Nonsynonymous SNV p.D83E	RJ20	1.20	27
chr6	114274545	G	A	*HDAC2*	Nonsynonymous SNV p.H179Y	RJ20	1.10	46
chr7	6018308	T	A	*PMS2*	Nonsynonymous SNV p.T732S	FY3	1.60	11
chr7	6043351	C	T	*PMS2*	Nonsynonymous SNV p.G108E	RJ20	1.30	59
chr7	6042213	C	G	*PMS2*	—	SY26	12.70	175
chr10	89692922	T	C	*PTEN*	Nonsynonymous SNV p.C136R	ZR2	44.20	539
chr10	89720799	TA	CTTTAACAAAA AATGATCTTA CTTTAACAAA AAATATCTTACT TTAACAAAAA ATTTTTTTGT TTACTTAAAG TAAAATAT	*PTEN*	Frameshift substitution p.V317fs	RJ38	35.00	268
chr10	89692905	G	A	*PTEN*	Nonsynonymous SNV p.R130Q	BYY24	32.40	968
chr10	89690802	G	C	*PTEN*	Splicing	BYY9	27.60	540
chr10	89711900	G	A	*PTEN*	Nonsynonymous SNV p.R173H	BYY9	26.00	1,079
chr10	89624238	CATCAAAGAG	—	*PTEN*	Frameshift deletion p.I5fs	WY12	23.50	475
chr10	89711904	TG	—	*PTEN*	Frameshift deletion p.Y176fs	RJ102	19.30	772
chr10	89720727	G	T	*PTEN*	Nonsynonymous SNV p.G293V	XJ6	18.00	94
chr10	89692905	G	A	*PTEN*	Nonsynonymous SNV p.R130Q	BYY12	11.80	404
chr10	89692981	T	—	*PTEN*	Stopgain p.Y155X	BYY10	9.50	91
chr10	89711894	A	C	*PTEN*	Nonsynonymous SNV p.Q171P	BYY17	5.50	108
chr10	89717672	C	T	*PTEN*	Stopgain p.R233X	RJ113-2	5.00	56
chr10	89711894	A	C	*PTEN*	Nonsynonymous SNV p.Q171P	XJ2	4.00	141
chr10	89624296	G	C	*PTEN*	Nonsynonymous SNV p.D24H	RJ143	3.40	29
chr10	89692956	AGGCACAAG	—	*PTEN*	Nonframeshift deletion p.Q149_A151del	RJ45	3.20	77
chr10	89692838	C	T	*PTEN*	Nonsynonymous SNV p.L108F	RJ134	2.50	36
chr10	89720786	AAGGAA TATCTAGT	—	*PTEN*	Frameshift deletion p.K313fs	WY2	2.10	33
chr10	89717741	G	T	*PTEN*	Stopgain p.E256X	SY9	2.00	18
chr10	89653805	A	G	*PTEN*	Nonsynonymous SNV p.M35V	SY9	1.80	13
chr10	89720859	T	A	*PTEN*	Nonsynonymous SNV p.F337Y	RJ26	1.20	20
chr10	89690846	—	CATATTATTT AGAGACAA	*PTEN*	Nonframeshift insertion p.V85delinsAYYLETI	RJ137	1.20	21
chr10	89720862	C	A	*PTEN*	Nonsynonymous SNV p.S338Y	RJ26	1.10	19
chr10	89720847	CCAACCGAT	—	*PTEN*	Nonframeshift deletion p.A333_Y336delinsD	RJ26	1.10	20
chr10	89720783	G	A	*PTEN*	Nonsynonymous SNV p.D312N	RJ112-1	1.10	39
chr10	89692849	G	T	*PTEN*	Nonsynonymous SNV p.W111C	RJ20	1.10	58
chr10	89624252	T	A	*PTEN*	Nonsynonymous SNV p.V9D	SY19	1.10	13
chr10	89711982	T	—	*PTEN*	Frameshift deletion p.F200fs	SY5	1.80	11
chr11	108098616	G	C	*ATM*	Splicing	FY5	59.50	355
chr11	108196272	G	T	*ATM*	Splicing	RJ74	44.50	575

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eTable 5. All Filtered Somatic Mutations and Deleterious Germline Mutations Detected (cont.)

Chromosome	Position	Ref	Alteration	Gene	Effect	Patient ID	Allele (%)	Alt DP
chr11	94204767	G	T	*MRE11*	Nonsynonymous SNV p.S273Y	RJ139	42.20	991
chr11	108158414	C	T	*ATM*	Stopgain p.Q1361X	BYY24	35.30	652
chr11	108124767	G	C	*ATM*	Splicing	RJ23-2	33.70	897
chr11	108115634	CTTTG	—	*ATM*	Frameshift deletion p.L263fs	RJ37	20.80	451
chr11	108206650	G	T	*ATM*	Stopgain p.E2744X	WY10	17.60	425
chr11	108121625	C	A	*ATM*	Stopgain p.S478X	RJ63	13.70	289
chr11	113934488	A	G	*ZBTB16*	Nonsynonymous SNV p.I156V	RJ152	13.20	603
chr11	108200991	G	A	*ATM*	Nonsynonymous SNV p.R2453H	ZZ6	10.20	124
chr11	108160424	—	T	*ATM*	Frameshift insertion p.V1446fs	RJ109-1	5.30	245
chr11	108160424	—	T	*ATM*	Frameshift insertion p.V1446fs	RJ109-2	3.30	35
chr11	108098606	—	CCTCAGAA ACTTAAA	*ATM*	Nonframeshift insertion p.A59_V60insLRNLN	RJ20	2.10	28
chr11	108198439	C	T	*ATM*	Nonsynonymous SNV p.T2348M	RJ29	1.50	46
chr11	108114700	A	T	*ATM*	Nonsynonymous SNV p.R173W	RJ52	1.50	10
chr11	94197398	T	C	*MRE11*	Nonsynonymous SNV p.Y369C	RJ82	1.50	24
chr11	108114719	C	A	*ATM*	Stopgain p.S179X	RJ19	1.30	28
chr11	114113039	G	A	*ZBTB16*	Nonsynonymous SNV p.R535H	RJ104-1	1.20	33
chr11	108098542	G	T	*ATM*	Stopgain p.E38X	RJ113-2	1.20	10
chr11	108186630	—	GAATGGAA TGGAATGTA ATGGAGAGT AAGGGAGTG GAATAGAAACA ATCCGAATGTA ATGGAATGGA ACGGAATGCAA TGGAATGGAAT GGAATGGAATGG	*ATM*	Stopgain p.P2029_ I2030delins PEWNGMX	RJ20	1.20	38
chr11	108192080	C	A	*ATM*	Nonsynonymous SNV p.L2169I	RJ20	1.10	54
chr11	108117837	G	A	*ATM*	Nonsynonymous SNV p.A350T	RJ20	1.10	33
chr11	108201123	T	A	*ATM*	Nonsynonymous SNV p.V2497D	SY6	1.00	15
chr11	108202285	G	C	*ATM*	Splicing	RJ157	57.70	965
chr11	108170527	A	C	*ATM*	Nonsynonymous SNV p.K1698Q	RJ24	1.00	19
chr12	133220142	G	A	*POLE*	Nonsynonymous SNV p.P1432L	BYY12	18.50	590
chr12	133219144	G	A	*POLE*	Nonsynonymous SNV p.R1634C	RJ108-2	17.40	695
chr12	124812065	G	—	*NCOR2*	Frameshift deletion p.P2358fs	RJ115	17.40	419
chr12	124819809	C	T	*NCOR2*	Nonsynonymous SNV p.G2095R	BYY12	15.00	581
chr12	133225959	G	A	*POLE*	Nonsynonymous SNV p.T1313M	RJ51	14.90	696
chr12	124810826	G	C	*NCOR2*	Nonsynonymous SNV p.P2425R	RJ111-1	13.70	839
chr12	124841323	C	T	*NCOR2*	Nonsynonymous SNV p.A1036T	ZZ6	4.90	92

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eTable 5. All Filtered Somatic Mutations and Deleterious Germline Mutations Detected (cont.)

Chromosome	Position	Ref	Alteration	Gene	Effect	Patient ID	Allele (%)	Alt DP
chr12	133249316	G	A	*POLE*	Nonsynonymous SNV p.T528M	BYY17	3.60	124
chr12	124856968	T	G	*NCOR2*	Nonsynonymous SNV p.T803P	BYY14	3.10	41
chr12	124829301	C	G	*NCOR2*	Nonsynonymous SNV p.G1519A	RJ55	2.10	35
chr12	124887094	—	GCTGCG	*NCOR2*	Nonframeshift insertion p.Q498_Q499insPQ	RJ80	2.00	19
chr12	124832801	G	—	*NCOR2*	Frameshift deletion p.H1302fs	ZZ7	1.60	18
chr12	124826590	G	A	*NCOR2*	Nonsynonymous SNV p.A1656V	WY25	1.30	23
chr12	124821617	C	T	*NCOR2*	Nonsynonymous SNV p.V1933I	ZZ6	1.30	32
chr12	124887093	—	TGG	*NCOR2*	Nonframeshift insertion p.Q498_Q499insH	RJ33	1.20	18
chr12	124829409	G	A	*NCOR2*	Nonsynonymous SNV p.T1483M	ZZ6	1.20	27
chr12	124832801	G	—	*NCOR2*	Frameshift deletion p.H1302fs	RJ117	1.10	25
chr12	124832801	G	—	*NCOR2*	Frameshift deletion p.H1302fs	XJ9	1.10	24
chr12	124832801	G	—	*NCOR2*	Frameshift deletion p.H1302fs	RJ141	1.10	39
chr12	124832832	C	A	*NCOR2*	Nonsynonymous SNV p.K1291N	RJ141	1.10	56
chr12	124832831	C	A	*NCOR2*	Stopgain p.E1292X	RJ141	1.10	56
chr12	124887093	—	TGCTGCTGG	*NCOR2*	Nonframeshift insertion p.Q498_Q499insHQQ	ZR1	1.10	28
chr12	124819159	A	C	*NCOR2*	Nonsynonymous SNVp.V2139G	RJ157	1.90	37
chr13	48955572	G	A	*RB1*	Stopgain p.W563X	RJ38	60.80	651
chr13	48939033	A	G	*RB1*	Nonsynonymous SNV p.K289E	RJ115	31.80	212
chr13	32945148	A	—	*BRCA2*	Frameshift deletion p.K2849fs	SY4	31.60	513
chr13	32910476	TCTTTTG GGACAAT	—	*BRCA2*	Frameshift deletion p.F663fs	FY3	26.10	139
chr13	49030487	T	C	*RB1*	Splicing	RJ44	25.50	709
chr13	103518708	G	A	*ERCC5*	Nonsynonymous SNV p.G766R	WY6	21.90	453
chr13	32906603	A	—	*BRCA2*	Frameshift deletion p.I332fs	RJ1	21.20	824
chr13	103518708	G	A	*ERCC5*	Nonsynonymous SNV p.G766R	BYY12	17.30	605
chr13	32893238	G	T	*BRCA2*	Nonsynonymous SNV p.W31L	RJ2	16.60	1,156
chr13	48939053	TTTTATACCT	—	*RB1*	Frameshift deletion p.F296fs	ZZ25	15.50	36
chr13	32911322	A	G	*BRCA2*	Nonsynonymous SNV p.K944E	RJ143	15.20	245
chr13	48934167	ATGGAAG	—	*RB1*	Frameshift deletion p.E209fs	WY13	14.30	132
chr13	32945228	G	A	*BRCA2*	Nonsynonymous SNV p.E2875K	RJ2	13.90	592
chr13	48919314	C	—	*RB1*	Frameshift deletion p.A160fs	BYY11	9.90	210
chr13	32914070	A	—	*BRCA2*	Frameshift deletion p.V1862fs	RJ68	8.40	99
chr13	32913836	—	A	*BRCA2*	Frameshift insertion p.N1784fs	RJ62	6.10	88
chr13	49030367	—	A	*RB1*	Frameshift insertion p.G617fs	BYY14	5.10	98
chr13	32931944	G	T	*BRCA2*	Nonsynonymous SNV p.Q2561H	FY4	4.40	68
chr13	49037963	G	A	*RB1*	Nonsynonymous SNV p.V735I	RJ20	3.40	47
chr13	48919256	AGTACCAA	—	*RB1*	Frameshift deletion p.T142fs	SY18	3.10	25

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eTable 5. All Filtered Somatic Mutations and Deleterious Germline Mutations Detected (cont.)

Chromosome	Position	Ref	Alteration	Gene	Effect	Patient ID	Allele (%)	Alt DP
chr13	49027168	C	T	*RB1*	Stopgain p.R579X	ZZ26	2.70	23
chr13	32912895	C	T	*BRCA2*	Nonsynonymous SNV p.S1468F	RJ20	2.50	68
chr13	48936968	AT	—	*RB1*	Frameshift deletion p.I246fs	BYY24	2.00	58
chr13	32914782	C	T	*BRCA2*	Nonsynonymous SNV p.T2097M	RJ112-1	1.80	80
chr13	32936658	A	T	*BRCA2*	Splicing	RJ26	1.40	21
chr13	103504584	C	T	*ERCC5*	Stopgain p.R69X	BYY12	1.30	34
chr13	48923150	—	G	*RB1*	Frameshift insertion p.L200fs	RJ106-1	1.20	30
chr13	49033917	A	C	*RB1*	Nonsynonymous SNVp.Q685P	RJ158	18.60	387
chr13	32912455	T	G	*BRCA2*	Nonsynonymous SNV p.D1321E	RJ24	1.20	22
chr13	32900282	A	T	*BRCA2*	Nonsynonymous SNV p.K157M	RJ81	1.20	24
chr13	32914409	AAT	—	*BRCA2*	Nonframeshift deletion p.N1973del	RJ24	1.10	27
chr13	32913793	—	GAAATTAGCCA GGCATGGTGGC ATATGCCTGT AGTCCTAG	*BRCA2*	Frameshift insertion p.L1768fs	RJ20	1.00	37
chr13	32931989	A	—	*BRCA2*	Frameshift deletion p.G2578fs	RJ19	1.00	34
chr14	38061173	CGGCTGCTT CTCGCACT TGAAGCG	—	*FOXA1*	Nonframeshift deletion p.R265_P272del	RJ25	48.90	3,487
chr14	38061223	TCTCGA	—	*FOXA1*	Nonframeshift deletion p.F254_N256delinsY	BYY5	42.50	1,788
chr14	38061191	G	C	*FOXA1*	Nonsynonymous SNV p.F266L	BYY18	35.10	2,136
chr14	38061220	CGTTCT	—	*FOXA1*	Nonframeshift deletion p.E255_N256del	RJ122	34.20	2,224
chr14	38060785	T	A	*FOXA1*	Nonsynonymous SNV p.I402F	RJ101	29.40	1,252
chr14	38061228	A	—	*FOXA1*	Frameshift deletion p.F254fs	FY5	29.40	620
chr14	38060784	A	G	*FOXA1*	Nonsynonymous SNV p.I402T	RJ101	29.10	1,245
chr14	38061163	CGCCGGCC CCCGGCTGCT TCTCGCACTTGA	—	*FOXA1*	Nonframeshift deletion p.F266_G276delinsC	SY7	26.90	779
chr14	38060860	GTGCCGG	—	*FOXA1*	Frameshift deletion p.P375fs	RJ65	26.00	614
chr14	68331719	G	T	*RAD51B*	Splicing	RJ150	25.70	45
chr14	38061249	T	C	*FOXA1*	Nonsynonymous SNV p.H247R	ZR2	24.50	264
chr14	38061157	CCCCGCCGC CGGCCCCCGG CTGCTTCTCGC ACTTGAAGCGC TTCT	—	*FOXA1*	Nonframeshift deletion p.Q263_G278delinsR	RJ131	22.30	563
chr14	38061240	GAGT	—	*FOXA1*	Frameshift deletion p.D249fs	BYY9	22.00	1,501
chr14	38061241	AGTC	—	*FOXA1*	Frameshift deletion p.D249fs	RJ124	20.90	1,568
chr14	38061178	GCTTCTCGC ACTTGAAGC	—	*FOXA1*	Nonframeshift deletion p.R265_K270del	RJ86	20.50	809
chr14	38061240	G	A	*FOXA1*	Nonsynonymous SNV p.S250F	WY6	20.10	522
chr14	38061249	T	C	*FOXA1*	Nonsynonymous SNV p.H247R	WY13	19.30	328
chr14	38061225	TCGAACATGTTG	—	*FOXA1*	Nonframeshift deletion p.M253_N256del	WY15	18.90	348

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eTable 5. All Filtered Somatic Mutations and Deleterious Germline Mutations Detected (cont.)

Chromosome	Position	Ref	Alteration	Gene	Effect	Patient ID	Allele (%)	Alt DP
chr14	38061223	TCTCGA	—	*FOXA1*	Nonframeshift deletion p.F254_N256delinsY	RJ27	18.40	1,267
chr14	38061233	GTTGCCGGA	—	*FOXA1*	Nonframeshift deletion p.S250_N252del	BYY24	18.40	834
chr14	38061208	—	CT	*FOXA1*	Frameshift insertion p.R261fs	RJ138	16.20	949
chr14	38061225	TCGAACATGTTG	—	*FOXA1*	Nonframeshift deletion p.M253_N256del	ZZ9	14.20	493
chr14	38061192	AAGCGCTTC	—	*FOXA1*	Nonframeshift deletion p.Q263_F266delinsH	RJ83	14.00	608
chr14	38061196	GCTT	—	*FOXA1*	Frameshift deletion p.K264fs	RJ7	13.60	758
chr14	38060770	A	G	*FOXA1*	Nonsynonymous SNV p.S407P	RJ87	11.50	586
chr14	38061220	CGTTCTCGAACA	—	*FOXA1*	Nonframeshift deletion p.M253_G257delinsS	RJ23-2	11.50	651
chr14	38061208	G	C	*FOXA1*	Nonsynonymous SNV p.R261G	WY19	11.30	197
chr14	38061191	G	C	*FOXA1*	Nonsynonymous SNV p.F266L	RJ115	11.10	332
chr14	38061214	AGCAGCC GTTCTCGA ACATGTTGC	—	*FOXA1*	Nonframeshift deletion p.G251_Y259delinsD	WY18	10.30	149
chr14	38061204	C	T	*FOXA1*	Nonsynonymous SNV p.R262H	RJ87	10.10	517
chr14	38061250	G	T	*FOXA1*	Nonsynonymous SNV p.H247N	RJ32	9.40	187
chr14	38060667	CTGC	—	*FOXA1*	Frameshift deletion p.G440fs	RJ94	9.00	261
chr14	38061207	C	T	*FOXA1*	Nonsynonymous SNV p.R261H	ZZ22	9.00	296
chr14	38061195	CGCTTCTG GCGGCGCAA GTAGCAGCCGTT CTCGAACATG TTGCCGGAGT	—	*FOXA1*	Frameshift deletion p.D249fs	RJ153	8.70	249
chr14	38061226	CGAACATGTTGC	—	*FOXA1*	Nonframeshift deletion p.G251_F254del	SY18	8.60	290
chr14	38061227	GAA	—	*FOXA1*	Nonframeshift deletion p.F254del	RJ110-1	8.10	387
chr14	38061155	GCCCCCGC CGCCGGCC CCCGGCTGCT TCTCGCACTTGAA	—	*FOXA1*	Nonframeshift deletion p.F266_G278del	RJ63	8.00	196
chr14	38061218	GCCGTT CTCGAACATG TTGCCGGAG	—	*FOXA1*	Frameshift deletion p.S250fs	RJ114-2	7.10	241
chr14	38061205	G	A	*FOXA1*	Nonsynonymous SNV p.R262C	ZR3	6.90	134
chr14	38061185	GCACTTGAA GCGCTTCT GGCG	—	*FOXA1*	Nonframeshift deletion p.R262_C268del	RJ40	6.60	364
chr14	38061213	T	C	*FOXA1*	Nonsynonymous SNV p.Y259C	RJ31	6.00	649
chr14	38061192	A	G	*FOXA1*	Nonsynonymous SNV p.F266S	RJ109-1	5.80	739
chr14	38061208	G	T	*FOXA1*	Nonsynonymous SNV p.R261S	BYY11	5.60	300
chr14	38061185	GCACTTGAA GCGCTTCTG	—	*FOXA1*	Nonframeshift deletion p.Q263_C268del	BYY10	5.40	115
chr14	38061215	GCAGCCGT TCTCGAACA TGTT	—	*FOXA1*	Nonframeshift deletion p.N252_C258del	WY7	5.10	68

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eTable 5. All Filtered Somatic Mutations and Deleterious Germline Mutations Detected (cont.)

Chromosome	Position	Ref	Alteration	Gene	Effect	Patient ID	Allele (%)	Alt DP
chr14	38061164	GCCGGC CCCCGGCT GCTTCTCGCA CTTGAA	—	*FOXA1*	Nonframeshift deletion p.F266_G275del	ZZ20	4.50	184
chr14	75497277	C	A	*MLH3*	Nonsynonymous SNV p.G1319V	ZZ14	4.40	133
chr14	38061194	—	CTT	*FOXA1*	Nonframeshift insertion p.R265_F266insS	RJ55	4.20	65
chr14	38061191	G	T	*FOXA1*	Nonsynonymous SNV p.F266L	RJ104-1	3.90	111
chr14	38061203	GCGGCGC AAGTAGCA	—	*FOXA1*	Nonframeshift deletion p.C258_R262del	RJ71	3.40	111
chr14	38061202	G	A	*FOXA1*	Stopgain p.Q263X	RJ4	3.20	324
chr14	38061192	A	G	*FOXA1*	Nonsynonymous SNV p.F266S	RJ109-2	2.90	115
chr14	38061151	TCCCGCCCC CGCCGCCGG CCCCCGGCTGC TTCTCGC ACTTGA	—	*FOXA1*	Nonframeshift deletion p.F266_S280delinsC	RJ68	2.60	38
chr14	38061227	GAACATGT TGCCGGA	—	*FOXA1*	Nonframeshift deletion p.S250_F254del	FY4	2.50	109
chr14	38061193	—	GCGCTTCTG	*FOXA1*	Nonframeshift insertion p.Q263_R265dup	RJ62	2.50	32
chr14	38061193	A	C	*FOXA1*	Nonsynonymous SNV p.F266V	RJ129	2.50	55
chr14	38061136	TGCCCCCGC TTCCGCTCCC GCCCCCGCCGC CGGCCCCCGGC TGCTTCTCGCA CTTGAAGCGCT	—	*FOXA1*	Nonframeshift deletion p.K264_G284del	BYY3	2.40	110
chr14	38061249	T	C	*FOXA1*	Nonsynonymous SNV p.H247R	RJ48	2.40	50
chr14	38061210	A	G	*FOXA1*	Nonsynonymous SNV p.L260S	RJ107-1	2.20	213
chr14	38061218	GCCGTTCTCGAAC	—	*FOXA1*	Frameshift deletion p.M253fs	RJ145	1.70	31
chr14	38061222	—	TC	*FOXA1*	Frameshift insertion p.N256fs	BYY17	1.70	60
chr14	38061191	G	T	*FOXA1*	Nonsynonymous SNV p.F266L	RJ104-2	1.50	11
chr14	38061192	A	C	*FOXA1*	Nonsynonymous SNV p.F266C	RJ22-2	1.50	100
chr14	38061249	T	C	*FOXA1*	Nonsynonymous SNV p.H247R	RJ80	1.50	42
chr14	38061193	—	GCGCTTCTGGCG	*FOXA1*	Nonframeshift insertion p.R262_R265dup	RJ47	1.30	29
chr14	38061249	T	C	*FOXA1*	Nonsynonymous SNV p.H247R	RJ121	1.30	55
chr14	38061229	ACATGTT	—	*FOXA1*	Frameshift deletion p.N252fs	RJ77	1.20	76
chr14	38061249	T	C	*FOXA1*	Nonsynonymous SNV p.H247R	ZZ11	1.20	33
chr14	38061221	GTTCTCGAA CATGTTGCCGGA	—	*FOXA1*	Nonframeshift deletion p.S250_N256del	RJ18	1.10	124
chr14	38061200	CTGGCGGCG	—	*FOXA1*	Nonframeshift deletion p.R261_Q263del	RJ157	23.40	1,246
chr15	41021753	A	G	*RAD51*	Nonsynonymous SNV p.Y233C	WY25	1.00	33
chr16	23647232	G	—	*PALB2*	Frameshift deletion p.P212fs	FY3	28.10	265
chr16	68835781	C	—	*CDH1*	Frameshift deletion p.P126fs	RJ108-2	25.00	631
chr16	23647133	G	A	*PALB2*	Nonsynonymous SNV p.A245V	RJ123	12.30	468
chr16	89825027	G	A	*FANCA*	Nonsynonymous SNV p.A980V	XJ2	10.30	428
chr16	68847375	G	A	*CDH1*	Nonsynonymous SNV p.D433N	RJ74	5.60	184

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eTable 5. All Filtered Somatic Mutations and Deleterious Germline Mutations Detected (cont.)

Chromosome	Position	Ref	Alteration	Gene	Effect	Patient ID	Allele (%)	Alt DP
chr16	68847399	G	T	*CDH1*	Splicing	RJ68	5.50	96
chr16	68772290	GA	—	*CDH1*	Frameshift deletion p.G49fs	WY10	4.80	18
chr16	23614808	C	G	*PALB2*	Nonsynonymous SNV p.G1178A	BYY5	3.30	69
chr16	23632742	C	G	*PALB2*	Nonsynonymous SNV p.E1018D	RJ74	3.00	125
chr16	23641351	TAAAGGAGTA	—	*PALB2*	Frameshift deletion p.Y705fs	SY18	2.70	72
chr16	68863656	C	G	*CDH1*	Nonsynonymous SNV p.P799A	RJ112-2	2.30	37
chr16	14026126	—	TCGAATG GAATGG	*ERCC4*	Frameshift insertion p.I363fs	RJ20	2.20	67
chr16	14042044	G	A	*ERCC4*	Nonsynonymous SNV p.R864H	RJ89	1.70	22
chr16	14041512	G	T	*ERCC4*	Nonsynonymous SNV p.D687Y	RJ4	1.60	139
chr16	14029552	T	C	*ERCC4*	Nonsynonymous SNV p.V588A	XJ2	1.30	63
chr16	14014062	C	T	*ERCC4*	Nonsynonymous SNV p.P14S	ZZ1	1.30	10
chr16	14024643	—	GGGA	*ERCC4*	Frameshift insertion p.I290fs	RJ112-1	1.20	53
chr16	23641613	G	T	*PALB2*	Nonsynonymous SNV p.P621H	FY7	1.10	79
chr17	7578400	G	T	*TP53*	Nonsynonymous SNV p.P177H	RJ118	72.40	1,959
chr17	37619140	—	CA	*CDK12*	Frameshift insertion p.Q273fs	RJ131	72.10	1,417
chr17	7578181	GGCGG CTCATAG	—	*TP53*	Nonframeshift deletion p.Y220_P223del	WY4	70.80	1,929
chr17	7576927	C	T	*TP53*	Splicing	RJ118	70.80	1,434
chr17	7577505	T	A	*TP53*	Nonsynonymous SNV p.D259V	RJ111-2	70.20	746
chr17	7574003	G	A	*TP53*	Stopgain p.R342X	RJ33	69.10	1,124
chr17	37646961	C	T	*CDK12*	Stopgain p.Q695X	RJ123	65.10	3,491
chr17	37666015	G	T	*CDK12*	Splicing	RJ143	63.20	1,676
chr17	7577539	G	A	*TP53*	Nonsynonymous SNV p.R248W	ZZ21	62.40	1,587
chr17	7577114	C	G	*TP53*	Nonsynonymous SNV p.C275S	ZR6	62.20	801
chr17	37618588	CTTCAAACTA GACCGAAGG	—	*CDK12*	Frameshift deletion p.F89fs	RJ133	57.20	1,609
chr17	37627561	—	A	*CDK12*	Frameshift insertion p.D494fs	RJ101	56.20	2,205
chr17	7579510	ACCTGGGT CTTCAGTGA	—	*TP53*	Frameshift deletion p.F54fs	RJ70	51.90	600
chr17	37627171	T	G	*CDK12*	Stopgain p.Y362X	RJ83	49.90	3,540
chr17	37627313	G	—	*CDK12*	Frameshift deletion p.A410fs	ZZ14	49.60	2,849
chr17	7578190	T	C	*TP53*	Nonsynonymous SNV p.Y220C	SY7	48.20	1,363
chr17	7577536	T	A	*TP53*	Nonsynonymous SNV p.R249W	ZR5	42.50	373
chr17	7577509	C	A	*TP53*	Stopgain p.E258X	RJ135	42.40	283
chr17	37619246	—	GACGGTC	*CDK12*	Frameshift insertion p.S311fs	XJ7	39.00	1,597
chr17	7578176	C	A	*TP53*	Splicing	RJ73	37.50	783
chr17	7578272	G	T	*TP53*	Nonsynonymous SNV p.H193N	RJ115	36.60	839
chr17	37627378	—	A	*CDK12*	Frameshift insertion p.N432fs	XJ6	36.30	1,371
chr17	37618727	G	T	*CDK12*	Stopgain p.E135X	XJ7	36.20	1,509
chr17	7579358	C	A	*TP53*	Nonsynonymous SNV p.R110L	RJ65	36.10	730
chr17	7578370	C	A	*TP53*	Splicing	RJ76	35.30	814

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eTable 5. All Filtered Somatic Mutations and Deleterious Germline Mutations Detected (cont.)

Chromosome	Position	Ref	Alteration	Gene	Effect	Patient ID	Allele (%)	Alt DP
chr17	47696426	A	G	*SPOP*	Nonsynonymous SNV p.F133L	RJ139	35.00	890
chr17	47696644	A	C	*SPOP*	Nonsynonymous SNV p.F102V	ZZ21	35.00	1,639
chr17	47696432	A	G	*SPOP*	Nonsynonymous SNV p.W131R	RJ105-2	34.70	1,328
chr17	7577085	C	A	*TP53*	Stopgain p.E285X	WY12	34.50	907
chr17	47696644	A	C	*SPOP*	Nonsynonymous SNV p.F102V	WY21	34.30	629
chr17	47696424	G	C	*SPOP*	Nonsynonymous SNV p.F133L	ZZ19	33.90	2,373
chr17	7576857	A	C	*TP53*	Nonsynonymous SNV p.L330R	BYY24	32.90	801
chr17	7577506	C	G	*TP53*	Nonsynonymous SNV p.D259H	WY21	32.50	452
chr17	56809886	C	T	*RAD51C*	Nonsynonymous SNV p.T336I	ZR6	32.10	467
chr17	7577022	G	A	*TP53*	Stopgain p.R306X	ZZ6	30.60	358
chr17	7577141	C	A	*TP53*	Nonsynonymous SNV p.G266V	SY20	30.50	607
chr17	7578280	G	A	*TP53*	Nonsynonymous SNV p.P190L	WY15	29.90	592
chr17	37646848	A	—	*CDK12*	Frameshift deletion p.E657fs	RJ94	29.30	830
chr17	15967502	C	A	*NCOR1*	Splicing	ZZ9	29.20	528
chr17	16004850	C	A	*NCOR1*	Stopgain p.E802X	BYY9	28.00	1,691
chr17	37682248	C	T	*CDK12*	Stopgain p.Q1147X	RJ141	27.50	1,810
chr17	37667797	—	A	*CDK12*	Frameshift insertion p.V896fs	WY10	27.20	583
chr17	47696467	C	T	*SPOP*	Nonsynonymous SNV p.S119N	RJ135	27.10	49
chr17	37665992	C	T	*CDK12*	Nonsynonymous SNV p.R882W	RJ73	26.60	779
chr17	37619128	TACC	—	*CDK12*	Frameshift deletion p.T269fs	WY3	26.40	1,004
chr17	37650948	G	A	*CDK12*	Splicing	RJ73	26.00	562
chr17	7577096	T	—	*TP53*	Frameshift deletion p.D281fs	WY6	25.50	598
chr17	37657677	TT	—	*CDK12*	Frameshift deletion p.L866fs	RJ138	25.40	480
chr17	41267768	T	C	*BRCA1*	Nonsynonymous SNV p.T37A	XJ6	24.70	299
chr17	7578504	AGGGCAGG TCTTGGCCAGT TGGCAAAACA TCTTGTTG	—	*TP53*	Frameshift deletion p.N131fs	BYY18	24.20	1,029
chr17	37619129	AC	—	*CDK12*	Frameshift deletion p.T269fs	RJ138	24.10	1,179
chr17	37646895	C	—	*CDK12*	Frameshift deletion p.P673fs	WY10	23.00	501
chr17	37667862	CCAT	—	*CDK12*	Frameshift deletion p.A916fs	WY3	22.90	510
chr17	7578526	C	A	*TP53*	Nonsynonymous SNV p.C135F	RJ88	22.80	649
chr17	47696431	C	G	*SPOP*	Nonsynonymous SNV p.W131S	RJ85	22.70	734
chr17	37627418	A	—	*CDK12*	Frameshift deletion p.K446fs	BYY14	22.10	757
chr17	37627733	CCTTT	—	*CDK12*	Frameshift deletion p.P550fs	XJ6	21.50	1,098
chr17	7578370	C	G	*TP53*	Splicing	RJ2	20.40	1,195
chr17	37646903	C	—	*CDK12*	Frameshift deletion p.P676fs	BYY14	20.30	619
chr17	7579580	G	A	*TP53*	Nonsynonymous SNV p.P36L	RJ108-2	20.30	665
chr17	47696424	G	C	*SPOP*	Nonsynonymous SNV p.F133L	WY24	20.20	189
chr17	37646970	—	A	*CDK12*	Stopgain p.Y698_K699delinsX	RJ120	20.00	740
chr17	7577534	C	G	*TP53*	Nonsynonymous SNV p.R249S	BYY26	20.00	480
chr17	47696424	G	C	*SPOP*	Nonsynonymous SNV p.F133L	BYY16	19.20	399

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eTable 5. All Filtered Somatic Mutations and Deleterious Germline Mutations Detected (cont.)

Chromosome	Position	Ref	Alteration	Gene	Effect	Patient ID	Allele (%)	Alt DP
chr17	37657671	C	A	*CDK12*	Nonsynonymous SNV p.S863Y	RJ3	19.10	962
chr17	37650890	AAC	—	*CDK12*	Nonframeshift deletion p.N788del	RJ3	18.60	719
chr17	7576923	AGTGCTAGGA	—	*TP53*	Frameshift deletion p.A307fs	WY19	18.20	444
chr17	47696425	A	G	*SPOP*	Nonsynonymous SNV p.F133S	RJ76	18.10	632
chr17	47696426	A	C	*SPOP*	Nonsynonymous SNV p.F133V	RJ16	17.50	1,540
chr17	37627889	C	T	*CDK12*	Stopgain p.Q602X	RJ83	17.20	1,071
chr17	37618464	C	—	*CDK12*	Frameshift deletion p.K48fs	BYY3	17.10	478
chr17	47696426	A	C	*SPOP*	Nonsynonymous SNV p.F133V	RJ37	16.80	501
chr17	37628017	G	T	*CDK12*	Splicing	RJ152	16.80	644
chr17	37619299	—	C	*CDK12*	Frameshift insertion p.Y327fs	RJ87	15.80	603
chr17	37627424	T	—	*CDK12*	Frameshift deletion p.L447fs	RJ86	15.10	460
chr17	37667875	G	C	*CDK12*	Nonsynonymous SNV p.W920C	RJ87	14.60	342
chr17	47696425	A	C	*SPOP*	Nonsynonymous SNV p.F133C	BYY8	14.60	550
chr17	7577506	C	A	*TP53*	Nonsynonymous SNV p.D259Y	WY16	14.50	388
chr17	7579414	C	T	*TP53*	Stopgain p.W91X	BYY10	14.00	306
chr17	37627334	G	T	*CDK12*	Stopgain p.G417X	BYY3	13.80	452
chr17	7578475	G	A	*TP53*	Nonsynonymous SNV p.P152L	RJ152	13.80	528
chr17	7577022	G	A	*TP53*	Stopgain p.R306X	RJ14	13.40	1,139
chr17	37650878	C	T	*CDK12*	Stopgain p.R784X	ZZ14	12.70	511
chr17	7577570	C	T	*TP53*	Nonsynonymous SNV p.M237I	WY5	12.40	229
chr17	7577505	T	A	*TP53*	Nonsynonymous SNV p.D259V	RJ111-1	11.90	392
chr17	7577121	G	A	*TP53*	Nonsynonymous SNV p.R273C	BYY16	11.80	297
chr17	37646947	C	T	*CDK12*	Nonsynonymous SNV p.A690V	ZZ20	11.80	229
chr17	16024505	C	—	*NCOR1*	Frameshift deletion p.R572fs	RJ108-2	11.50	337
chr17	7577093	—	G	*TP53*	Frameshift insertion p.R282fs	WY19	10.60	271
chr17	37649020	TATG	—	*CDK12*	Frameshift deletion p.Y709fs	RJ120	10.60	353
chr17	16029446	T	—	*NCOR1*	Frameshift deletion p.E529fs	RJ108-2	10.40	99
chr17	37627570	G	—	*CDK12*	Frameshift deletion p.A497fs	BYY11	10.00	410
chr17	7578403	C	T	*TP53*	Nonsynonymous SNV p.C176Y	SY10	10.00	133
chr17	7578550	G	A	*TP53*	Nonsynonymous SNV p.S127F	SY18	10.00	177
chr17	37627619	—	T	*CDK12*	Frameshift insertion p.V513fs	RJ104-1	9.70	182
chr17	46805694	A	C	*HOXB13*	Nonsynonymous SNV p.Y88D	RJ135	9.70	223
chr17	47696601	G	C	*SPOP*	Nonsynonymous SNV p.A116G	RJ102	9.40	412
chr17	37619279	—	A	*CDK12*	Stopgain p.Y319_S320delinsX	BYY11	9.10	429
chr17	37618491	T	—	*CDK12*	Frameshift deletion p.V56fs	RJ31	9.10	778
chr17	37646821	CT	—	*CDK12*	Frameshift deletion p.L649fs	ZZ22	8.90	89
chr17	47696424	G	T	*SPOP*	Nonsynonymous SNV p.F133L	ZZ2	8.80	262
chr17	37619279	—	A	*CDK12*	Stopgain p.Y319_S320delinsX	RJ31	8.70	883
chr17	47696689	A	C	*SPOP*	Nonsynonymous SNV p.Y87D	RJ109-1	8.60	694
chr17	7579285	GGAAGCCA GCCCCTCAGG GCAACTGACC	—	*TP53*	Frameshift deletion p.T125fs	RJ124	7.90	400

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eTable 5. All Filtered Somatic Mutations and Deleterious Germline Mutations Detected (cont.)

Chromosome	Position	Ref	Alteration	Gene	Effect	Patient ID	Allele (%)	Alt DP
chr17	41246511	G	T	*BRCA1*	Nonsynonymous SNV p.P346H	WY7	7.70	18
chr17	37619141	C	T	*CDK12*	Stopgain p.Q273X	RJ143	7.70	364
chr17	7573986	G	—	*TP53*	Frameshift deletion p.L348fs	FY4	7.30	219
chr17	37619281	C	G	*CDK12*	Stopgain p.Y319X	RJ123	7.10	471
chr17	37646854	A	—	*CDK12*	Frameshift deletion p.E659fs	RJ152	6.70	396
chr17	7578508	C	T	*TP53*	Nonsynonymous SNV p.C141Y	ZZ18	6.60	205
chr17	7578235	T	C	*TP53*	Nonsynonymous SNV p.Y205C	ZZ24	6.60	306
chr17	37646961	C	T	*CDK12*	Stopgain p.Q695X	BYY4	6.40	129
chr17	47696424	G	C	*SPOP*	Nonsynonymous SNV p.F133L	XJ3	6.30	87
chr17	37687471	—	G	*CDK12*	Frameshift insertion p.T1463fs	RJ108-2	6.00	145
chr17	7577081	T	A	*TP53*	Nonsynonymous SNV p.E286V	ZZ8	5.90	155
chr17	37618445	A	T	*CDK12*	Stopgain p.K41X	ZZ20	5.70	101
chr17	37627619	—	T	*CDK12*	Frameshift insertion p.V513fs	RJ104-2	5.30	34
chr17	37667788	TTACACA AACAAAGTCA	—	*CDK12*	Frameshift deletion p.T893fs	RJ86	5.30	129
chr17	37676223	C	T	*CDK12*	Nonsynonymous SNV p.A993V	ZZ18	5.20	175
chr17	37650899	—	A	*CDK12*	Frameshift insertion p.I792fs	RJ77	4.90	35
chr17	16021203	T	A	*NCOR1*	Nonsynonymous SNV p.K685I	ZR4	4.60	79
chr17	37676207	A	G	*CDK12*	Splicing	BYY4	4.40	118
chr17	7578263	G	A	*TP53*	Stopgain p.R196X	ZZ4	4.40	144
chr17	37627315	T	—	*CDK12*	Frameshift deletion p.A411fs	RJ80	4.20	142
chr17	15961359	A	C	*NCOR1*	Stopgain p.Y2010X	RJ55	4.10	55
chr17	47696689	A	C	*SPOP*	Nonsynonymous SNV p.Y87D	RJ109-2	4.10	77
chr17	47696689	A	T	*SPOP*	Nonsynonymous SNV p.Y87N	SY9	4.00	51
chr17	47696425	A	C	*SPOP*	Nonsynonymous SNV p.F133C	RJ107-1	3.90	394
chr17	37627793	C	T	*CDK12*	Stopgain p.Q570X	RJ112-1	3.80	382
chr17	7577550	C	A	*TP53*	Nonsynonymous SNV p.G244V	SY9	3.80	56
chr17	7577517	A	C	*TP53*	Nonsynonymous SNV p.I255S	ZR4	3.80	69
chr17	37672045	C	T	*CDK12*	Stopgain p.Q944X	SY9	3.70	36
chr17	37619206	CTACGTAG	T	*CDK12*	Frameshift deletion p.Y295fs	RJ114-2	3.60	116
chr17	47679285	G	C	*SPOP*	Nonsynonymous SNV p.L308V	ZZ9	3.60	105
chr17	7577570	C	T	*TP53*	Nonsynonymous SNV p.M237I	WY26	3.50	69
chr17	37627919	C	T	*CDK12*	Stopgain p.Q612X	RJ114-2	3.40	88
chr17	37676226	TTGATTTA	—	*CDK12*	Frameshift deletion p.D995fs	RJ71	3.30	75
chr17	37666000	—	A	*CDK12*	Frameshift insertion p.N885fs	ZZ22	3.20	18
chr17	7577144	AGT	—	*TP53*	Nonframeshift deletion p.L265del	RJ137	3.10	108
chr17	37667852	T	G	*CDK12*	Nonsynonymous SNV p.Y913D	RJ11	2.80	191
chr17	47696601	G	C	*SPOP*	Nonsynonymous SNV p.A116G	RJ4	2.80	260
chr17	37627577	C	—	*CDK12*	Frameshift deletion p.Q498fs	WY20	2.80	11
chr17	16001704	G	A	*NCOR1*	Stopgain p.R933X	ZZ19	2.80	75
chr17	47696456	A	G	*SPOP*	Nonsynonymous SNV p.Y123H	RJ92	2.20	140
chr17	7579427	G	—	*TP53*	Frameshift deletion p.P87fs	RJ10	2.10	212
chr17	37657693	G	T	*CDK12*	Splicing	RJ11	2.00	127

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eTable 5. All Filtered Somatic Mutations and Deleterious Germline Mutations Detected (cont.)

Chromosome	Position	Ref	Alteration	Gene	Effect	Patient ID	Allele (%)	Alt DP
chr17	37650838	—	G	*CDK12*	Frameshift insertion p.A771fs	RJ40	2.00	73
chr17	37676249	ACAC	—	*CDK12*	Frameshift deletion p.T1002fs	RJ71	1.80	38
chr17	41245326	G	A	*BRCA1*	Nonsynonymous SNV p.S741F	RJ27	1.70	119
chr17	41245327	A	T	*BRCA1*	Nonsynonymous SNV p.S741T	RJ27	1.70	119
chr17	7577532	GGCCTCC	—	*TP53*	Frameshift deletion p.R248fs	RJ83	1.60	30
chr17	7579315	G	T	*TP53*	Stopgain p.C124X	WY25	1.60	42
chr17	7579408	CAGGGGCCA GGAGGGGGC TGGTG	—	*TP53*	Frameshift deletion p.A86fs	ZZ11	1.60	57
chr17	37687472	G	—	*CDK12*	Frameshift deletion p.G1461fs	ZZ7	1.50	17
chr17	37619180	C	T	*CDK12*	Stopgain p.Q286X	ZZ23	1.50	29
chr17	41219700	T	A	*BRCA1*	Stopgain p.K1667X	RJ88	1.40	23
chr17	15960847	C	—	*NCOR1*	Frameshift deletion p.V2125fs	RJ71	1.40	16
chr17	37627889	C	T	*CDK12*	Stopgain p.Q602X	RJ18	1.40	160
chr17	37687472	G	—	*CDK12*	Frameshift deletion p.G1461fs	RJ119	1.40	17
chr17	7579534	TTCAA	—	*TP53*	Frameshift deletion p.I50fs	RJ140	1.40	49
chr17	7579580	G	A	*TP53*	Nonsynonymous SNV p.P36L	RJ108-1	1.30	151
chr17	15968814	A	C	*NCOR1*	Nonsynonymous SNV p.Y1646D	RJ24	1.30	43
chr17	37619172	C	T	*CDK12*	Nonsynonymous SNV p.S283L	RJ66	1.20	20
chr17	41199713	T	A	*BRCA1*	Nonsynonymous SNV p.H1805L	FY3	1.20	27
chr17	41201161	G	T	*BRCA1*	Nonsynonymous SNV p.L1795I	RJ24	1.20	35
chr17	37657673	A	G	*CDK12*	Nonsynonymous SNV p.N864D	RJ80	1.20	25
chr17	59861762	T	A	*BRIP1*	Nonsynonymous SNV p.Q499H	RJ20	1.10	26
chr17	59861763	T	C	*BRIP1*	Nonsynonymous SNV p.Q499R	RJ20	1.10	26
chr17	15973692	TTCCCCG	—	*NCOR1*	Frameshift deletion p.R1432fs	RJ118	1.10	66
chr17	15974721	A	G	*NCOR1*	Splicing	BYY5	1.00	33
chr17	16075118	TT	—	*NCOR1*	Frameshift deletion p.K145fs	BYY17	1.00	21
chr17	7577147	AG	—	*TP53*	Frameshift deletion p.L264fs	SY26	40.60	788
chr17	7577548	C	T	*TP53*	Nonsynonymous SNVp.G245S	SY28	7.80	155
chr17	7577575	A	G	*TP53*	Nonsynonymous SNVp.Y236H	SY29	7.40	199
chr17	37619280	—	A	*CDK12*	Stopgain p.Y319_S320delinsX	SY30	1.00	26
chr17	37657610	CT	AA	*CDK12*	Nonsynonymous SNVp.L843K	SY30	1.50	17
chr17	47696644	A	C	*SPOP*	Nonsynonymous SNVp.F102V	SY5	1.50	19
chr19	50917071	G	T	*POLD1*	Nonsynonymous SNV p.G775W	RJ108-2	19.40	427
chr19	1207048	A	C	*STK11*	Nonsynonymous SNV p.I46L	SY10	6.30	71
chr19	50909469	G	T	*POLD1*	Nonsynonymous SNV p.A425S	WY12	2.20	80
chr19	50919866	G	—	*POLD1*	Frameshift deletion p.D987fs	RJ119	1.50	23
chr19	45855582	T	G	*ERCC2*	Nonsynonymous SNV p.K692T	SY11	1.20	11
chr19	50917071	G	T	*POLD1*	Nonsynonymous SNV p.G775W	RJ108-1	1.20	161
chr22	29095882	G	A	*CHEK2*	Nonsynonymous SNV p.R318C	RJ113-2	4.00	51

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eTable 5. All Filtered Somatic Mutations and Deleterious Germline Mutations Detected (cont.)

Chromosome	Position	Ref	Alteration	Gene	Effect	Patient ID	Allele (%)	Alt DP
chrX	66943552	A	G	*AR*	Nonsynonymous SNV p.T878A	BYY9	53.40	5,016
chrX	66943552	A	G	*AR*	Nonsynonymous SNV p.T878A	RJ141	50.00	1,199
chrX	66943543	C	T	*AR*	Nonsynonymous SNV p.H875Y	WY24	44.30	306
chrX	66943552	A	G	*AR*	Nonsynonymous SNV p.T878A	BYY5	42.40	587
chrX	66931463	T	A	*AR*	Nonsynonymous SNV p.L702H	RJ105-2	34.60	2,266
chrX	66937371	G	T	*AR*	Nonsynonymous SNV p.W742L	RJ139	33.20	585
chrX	66937371	G	T	*AR*	Nonsynonymous SNV p.W742L	RJ138	29.80	837
chrX	66943543	C	T	*AR*	Nonsynonymous SNV p.H875Y	RJ108-2	27.10	307
chrX	66943552	A	G	*AR*	Nonsynonymous SNV p.T878A	RJ29	24.50	765
chrX	66943543	C	T	*AR*	Nonsynonymous SNV p.H875Y	RJ51	23.40	278
chrX	66931463	T	A	*AR*	Nonsynonymous SNV p.L702H	RJ102	21.50	749
chrX	66937371	G	T	*AR*	Nonsynonymous SNV p.W742L	RJ85	21.10	390
chrX	66937372	G	C	*AR*	Nonsynonymous SNV p.W742C	BYY5	20.20	395
chrX	66937371	G	T	*AR*	Nonsynonymous SNV p.W742L	WY13	19.80	282
chrX	66943552	A	G	*AR*	Nonsynonymous SNV p.T878A	BYY12	19.10	330
chrX	66943552	A	G	*AR*	Nonsynonymous SNV p.T878A	RJ108-2	18.80	220
chrX	66937372	G	C	*AR*	Nonsynonymous SNV p.W742C	RJ153	16.10	339
chrX	66943543	C	T	*AR*	Nonsynonymous SNV p.H875Y	BYY12	16.00	278
chrX	66937372	G	C	*AR*	Nonsynonymous SNV p.W742C	RJ32	15.00	242
chrX	66931463	T	A	*AR*	Nonsynonymous SNV p.L702H	RJ122	15.00	1,443
chrX	66943552	A	G	*AR*	Nonsynonymous SNV p.T878A	RJ32	12.70	132
chrX	66937371	G	T	*AR*	Nonsynonymous SNV p.W742L	ZR5	12.30	154
chrX	66937370	T	C	*AR*	Nonsynonymous SNV p.W742R	RJ85	12.10	223
chrX	66943552	A	G	*AR*	Nonsynonymous SNV p.T878A	WY24	11.80	85
chrX	66943552	A	G	*AR*	Nonsynonymous SNV p.T878A	ZZ6	11.20	75
chrX	66943552	A	G	*AR*	Nonsynonymous SNV p.T878A	RJ107-1	10.80	677
chrX	66765158	T	A	*AR*	Nonsynonymous SNV p.L57Q	RJ101	9.50	73
chrX	66931463	T	A	*AR*	Nonsynonymous SNV p.L702H	RJ32	8.80	138
chrX	66937372	G	T	*AR*	Nonsynonymous SNV p.W742C	ZR4	8.70	128
chrX	66943552	A	G	*AR*	Nonsynonymous SNV p.T878A	RJ133	8.10	212
chrX	66937372	G	C	*AR*	Nonsynonymous SNV p.W742C	BYY11	7.50	257
chrX	66943552	A	G	*AR*	Nonsynonymous SNV p.T878A	ZR4	7.00	67
chrX	66937372	G	C	*AR*	Nonsynonymous SNV p.W742C	RJ138	6.40	168
chrX	66937371	G	T	*AR*	Nonsynonymous SNV p.W742L	RJ107-1	6.20	483
chrX	66931463	T	A	*AR*	Nonsynonymous SNV p.L702H	BYY5	5.90	135
chrX	66943553	C	G	*AR*	Nonsynonymous SNV p.T878S	RJ62	5.30	41
chrX	66937371	G	T	*AR*	Nonsynonymous SNV p.W742L	RJ114-2	5.10	84
chrX	66937372	G	T	*AR*	Nonsynonymous SNV p.W742C	XJ2	4.70	128

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eTable 5. All Filtered Somatic Mutations and Deleterious Germline Mutations Detected (cont.)

Chromosome	Position	Ref	Alteration	Gene	Effect	Patient ID	Allele (%)	Alt DP
chrX	66931504	G	A	*AR*	Nonsynonymous SNV p.V716M	ZZ6	4.40	44
chrX	66931463	T	A	*AR*	Nonsynonymous SNV p.L702H	RJ105-1	3.90	176
chrX	66937372	G	T	*AR*	Nonsynonymous SNV p.W742C	RJ149	3.50	50
chrX	66937372	G	C	*AR*	Nonsynonymous SNV p.W742C	ZR5	3.50	43
chrX	66931463	T	A	*AR*	Nonsynonymous SNV p.L702H	WY7	3.40	15
chrX	66931463	T	A	*AR*	Nonsynonymous SNV p.L702H	RJ71	3.30	46
chrX	66943552	A	G	*AR*	Nonsynonymous SNV p.T878A	RJ71	3.30	35
chrX	66937371	G	T	*AR*	Nonsynonymous SNV p.W742L	XJ2	3.30	90
chrX	66931463	T	A	*AR*	Nonsynonymous SNV p.L702H	RJ62	3.10	33
chrX	66937372	G	C	*AR*	Nonsynonymous SNV p.W742C	RJ134	3.00	46
chrX	66937372	G	T	*AR*	Nonsynonymous SNV p.W742C	RJ137	3.00	97
chrX	66943552	A	G	*AR*	Nonsynonymous SNV p.T878A	RJ134	3.00	32
chrX	66943552	A	G	*AR*	Nonsynonymous SNV p.T878A	RJ149	3.00	28
chrX	66937371	G	T	*AR*	Nonsynonymous SNV p.W742L	ZZ9	3.00	90
chrX	66943552	A	G	*AR*	Nonsynonymous SNV p.T878A	BYY13	2.90	12
chrX	66937372	G	C	*AR*	Nonsynonymous SNV p.W742C	ZZ26	2.90	72
chrX	66937372	G	T	*AR*	Nonsynonymous SNV p.W742C	BYY12	2.70	61
chrX	66937371	G	T	*AR*	Nonsynonymous SNV p.W742L	ZZ26	2.70	66
chrX	66937371	G	T	*AR*	Nonsynonymous SNV p.W742L	RJ10	2.60	147
chrX	66937372	G	C	*AR*	Nonsynonymous SNV p.W742C	RJ139	2.60	46
chrX	66905888	G	T	*AR*	Nonsynonymous SNV p.C602F	ZZ19	2.30	266
chrX	66937372	G	C	*AR*	Nonsynonymous SNV p.W742C	RJ104-1	2.20	39
chrX	66943552	A	G	*AR*	Nonsynonymous SNV p.T878A	RJ137	2.20	60
chrX	66937371	G	T	*AR*	Nonsynonymous SNV p.W742L	WY20	2.00	19
chrX	66765161	A	T	*AR*	Nonsynonymous SNV p.Q58L	SY8	1.90	28
chrX	66931463	T	A	*AR*	Nonsynonymous SNV p.L702H	RJ141	1.90	63
chrX	66937371	G	T	*AR*	Nonsynonymous SNV p.W742L	BYY11	1.80	64
chrX	66931463	T	A	*AR*	Nonsynonymous SNV p.L702H	ZZ14	1.80	93
chrX	66943552	A	G	*AR*	Nonsynonymous SNV p.T878A	SY12	1.70	18
chrX	66937372	G	T	*AR*	Nonsynonymous SNVp.W742C	SY28	22.90	479
chrX	66943552	A	G	*AR*	Nonsynonymous SNV p.T878A	RJ104-1	1.60	23
chrX	66943552	A	G	*AR*	Nonsynonymous SNV p.T878A	RJ62	1.60	12
chrX	66937372	G	C	*AR*	Nonsynonymous SNV p.W742C	RJ114-2	1.50	24
chrX	66943543	C	T	*AR*	Nonsynonymous SNV p.H875Y	RJ144	1.50	22
chrX	66937372	G	T	*AR*	Nonsynonymous SNV p.W742C	RJ101	1.40	124
chrX	66943585	A	G	*AR*	Nonsynonymous SNV p.S889G	RJ75	1.40	24

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eTable 5. All Filtered Somatic Mutations and Deleterious Germline Mutations Detected (cont.)

Chromosome	Position	Ref	Alteration	Gene	Effect	Patient ID	Allele (%)	Alt DP
chrX	66905791	G	A	*AR*	Nonsynonymous SNV p.R542Q	RJ112-1	1.30	27
chrX	66937372	G	C	*AR*	Nonsynonymous SNV p.W742C	ZR2	1.20	139
Deleterious germline mutations								
chr1	45800165	G	A	*MUTYH*	Stopgain p.R19X	RJ82	51.49	104
chr1	45800165	G	A	*MUTYH*	Stopgain p.R19X	RJ82	51.49	104
chr2	128051209	AA	—	*ERCC3*	Frameshift deletion p.V38fs	RJ41	46.41	207
chr2	17962331	—	T	*GEN1*	Frameshift insertion p.S619fs	RJ54	49.91	292
chr2	190738287	G	—	*PMS1*	Stopgain p.V847X	BYY13	50.63	161
chr2	215645974	—	T	*BARD1*	Frameshift insertion p.K209fs	ZZ10	49.07	290
chr2	47604177	—	C	*EPCAM*	Frameshift insertion p.R173fs	BYY25	47.71	292
chr2	17955667	C	T	*GEN1*	Stopgain p.R401X	XJ7	46.94	376
chr2	17955667	C	T	*GEN1*	Stopgain p.R401X	XJ7	46.94	376
chr3	142259780	G	A	*ATR*	Stopgain p.R1183X	RJ50	49.86	366
chr11	108115681	G	T	*ATM*	Stopgain p.E277X	RJ15	53.80	262
chr11	108236087	G	A	*ATM*	Nonsynonymous SNV p.R3008H	RJ25	48.47	190
chr11	108236087	G	A	*ATM*	Nonsynonymous SNV p.R3008H	XJ3	50.54	464
chr11	108121594	AA	—	*ATM*	Frameshift deletion p.K468fs	ZZ13	50.16	318
chr11	108178646	C	A	*ATM*	Stopgain p.C1899X	ZZ27	51.08	261
chr11	108214099	GTGA	—	*ATM*	Splicing	ZZ28	44.56	266
chr11	108121531	C	T	*ATM*	Stopgain p.R447X	WY22	49.76	513
chr13	32911298	AAAC	—	*BRCA2*	Frameshift deletion p.A938fs	RJ38	50.52	343
chr13	32911335	T	—	*BRCA2*	Frameshift deletion p.Y949fs	RJ16	50.44	344
chr13	32910749	T	—	*BRCA2*	Frameshift deletion p.Q754fs	RJ17	54.51	369
chr13	32914954	TCTC	—	*BRCA2*	Frameshift deletion p.S2156fs	RJ26	47.40	283
chr13	32914174	C	G	*BRCA2*	Stopgain p.Y1894X	WY13	51.04	713
chr13	32911143	CAGA	—	*BRCA2*	Frameshift deletion p.D885fs	BYY7	45.77	303
chr13	32914066	AATT	—	*BRCA2*	Frameshift deletion p.I1859fs	WY7	48.38	733
chr13	32911100	—	T	*BRCA2*	Frameshift insertion p.S871fs	ZR2	49.86	367
chr13	103514595	C	T	*ERCC5*	Stopgain p.R366X	ZZ7	46.07	299
chr13	32913017	C	T	*BRCA2*	Stopgain p.Q1509X	ZZ9	49.38	318
chr13	32915032	G	—	*BRCA2*	Frameshift deletion p.G2181fs	ZZ12	50.41	245
chr13	32936732	G	A	*BRCA2*	Stopgain p.W2626X	ZZ15	54.86	271
chr13	32911047	—	C	*BRCA2*	Frameshift insertion p.Q853fs	ZR6	47.65	284
chr13	32971034	G	T	*BRCA2*	Splicing	RJ119	43.55	223
chr13	32914130	AATA	—	*BRCA2*	Frameshift deletion p.K1881fs	XJ7	48.41	396
chr13	32910932	C	—	*BRCA2*	Frameshift deletion p.M815fs	RJ144	49.59	305
chr13	32914210	CT	—	*BRCA2*	Frameshift deletion p.L1908fs	SY21	51.00	637
chr13	32913558	—	A	*BRCA2*	Frameshift insertion p.W1692fs	RJ124	45.55	169
chr13	32921033	G	A	*BRCA2*	Nonsynonymous SNV p.R2336H	RJ117	49.55	164

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eTable 5. All Filtered Somatic Mutations and Deleterious Germline Mutations Detected (cont.)

Chromosome	Position	Ref	Alteration	Gene	Effect	Patient ID	Allele (%)	Alt DP
chr13	32907522	C	A	*BRCA2*	Stopgain p.S636X	RJ154	52.41	228
chr14	75515744	T	—	*MLH3*	Frameshift deletion p.D206fs	FY5	47.14	354
chr16	23641691	T	—	*PALB2*	Frameshift deletion p.D595fs	RJ45	45.96	625
chr16	23647108	—	A	*PALB2*	Frameshift insertion p.S254fs	RJ30	44.71	148
chr16	23614813	T	—	*PALB2*	Frameshift deletion p.D1177fs	FY2	50.27	277
chr16	23634318	C	A	*PALB2*	Stopgain p.E990X	ZZ25	46.28	137
chr17	41246566	AT	—	*BRCA1*	Frameshift deletion p.C328fs	RJ99	49.20	308
chr17	41245437	TT	—	*BRCA1*	Frameshift deletion p.N704fs	RJ91	43.00	86
chr17	56801451	C	T	*RAD51C*	Stopgain p.R319X	WY4	46.38	480
chr17	59876486	G	A	*BRIP1*	Stopgain p.R439X	ZR4	47.26	311
chr17	41197810	TGCCCAAT	—	*BRCA1*	Frameshift deletion p.I1824fs	SY19	40.40	202

Abbreviations: Alt, alteration; DP, depth; Ref, reference.

eTable 6. Genomic Alteration Status, PFS, and PSA Change Over 12 Weeks in 58 Patients With ctDNA Samples Collected Before Abiraterone Treatment

Patient	PFS (mo)	Censored	PSA Change Over 12 wk (%)	*CDK12* Defect	*BRCA2* Defect	*ATM* Defect	*TP53* Defect	*RB1* Defect	*AR* Gain	*AR* Mutation
RJ19	10.90	No	–76		*BRCA2:* p.G2578fs	*ATM:* p.S179X				
RJ21	12.80	No	–64							
RJ22-1	8.40	No	–57							
RJ27	3.27	No	87		*BRCA2:* loss				Yes	
RJ28	8.57	No	–34							
RJ30	13.00	No	–54							
RJ39	12.00	No	–36							
RJ40	4.00	No	24	*CDK12:* p.A771fs						
RJ42	4.00	No	13							
RJ43	5.00	No	–2							
RJ44	1.00	No	221					*RB1:* c.196+2T>C		
RJ47	12.00	No	–87							
RJ48	12.40	No	–76							
RJ49	13.00	No	–73							
RJ50	10.40	No	–63							
RJ51	10.00	No	–66							*AR:* p.H875Y
RJ53	3.00	No	125				*TP53:* loss			
RJ54	11.00	No	–83							
RJ56	14.60	No	–89							
RJ71	1.70	No	212	*CDK12:* p.D995fs, *CDK12:* p.T12fs						*AR:* p.L72H, *AR:* p.T878A
RJ75	14.00	No	–74							*AR:* p.S889G
RJ82	15.00	Yes	–66							
RJ86	12.00	Yes	–68	*CDK12:* p.L447fs, *CDK12:* p.T893fs						
RJ94	1.60	No	121	*CDK12:* p.E657fs					Yes	
RJ95	13.00	No	–79							
RJ98	9.00	No	–68							
RJ106-1	6.83	No	2					*RB1:* p. L2fs		
RJ109-1	7.00	No	–35			*ATM:* p.V1446fs			Yes	
RJ110-1	33.50	No	–93							
RJ113-1	14.00	No	–94							
RJ116	9.00	No	–96							
RJ117	4.00	Yes	–48		*gBRCA2:* p.R2336H					
RJ118	1.00	No	157	*CDK12:* loss			*TP53:* c.92-1G>A, *TP53:* p.P177H		Yes	

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eTable 6. Genomic Alteration Status, PFS, and PSA Change Over 12 Weeks in 58 Patients With ctDNA Samples Collected Before Abiraterone Treatment (cont.)

Patient	PFS (mo)	Censored	PSA Change Over 12 wk (%)	*CDK12* Defect	*BRCA2* Defect	*ATM* Defect	*TP53* Defect	*RB1* Defect	*AR* Gain	*AR* Mutation
RJ121	10.00	Yes	–79							
RJ125	4.00	Yes	–58							
RJ132	5.00	Yes	–46							
RJ143	1.00	No	72	*CDK12:* p.Q273X, *CDK12:* c.26 66+1G>T						
RJ150	3.00	Yes	22							
RJ151	2.00	Yes	113							
SY3	12.00	No	–77							
SY4	15.00	Yes	–87		*BRCA2:* p.K2849fs					
SY8	4.30	No	–18							
SY16	9.00	Yes	–67							
SY17	1.00	Yes	321							
SY19	7.00	Yes	–22							
SY20	6.00	No	–25				*TP53:* p.G266V			
SY21	3.00	No	67		*gBRCA2:* p.L198fs					
SY23	3.00	No	112							
BYY1	13.00	Yes	–87							
BYY10	6.50	No	–13				*TP53:* p.W91X			
BYY11	1.00	No	112	*CDK12:* p.A497fs				*RB1:* p.A16fs		*AR:* p.W742L, *AR:* p.W742C
BYY23	8.90	Yes	–65							
BYY5	9.70	No	–86							*AR:* p.W742L, *AR:* p.W742C
FY1	1.00	Yes	98							
FY3	5.00	Yes	–34		*BRCA2:* p.F663fs				Yes	
FY7	3.00	No	76							
XJ4	1.00	Yes	221							
ZZ18	1.00	No	321				*TP53:* p.C141Y			

Blank cells indicate no defect.
Abbreviations: ctDNA, circulating tumor DNA; g, germline; PFS, progression-free survival; PSA, prostate-specific antigen.

eTable 7. Genomic Alteration Status, PFS, and PSA Change Over 12 Weeks in 66 Patients With ctDNA Samples Collected Before Docetaxel Treatment

Patient	PFS (mo)	Censored	PSA Change Over 12 wks (%)	*CDK12* Defect	*BRCA2* Defect	*ATM* Defect	*TP53* Defect	*RB1* Defect	*AR* Gain	*AR* Mutation
RJ1	1.33	No	123		*BRCA2:* p.I332fs					
RJ2	2.10	No	211				*TP53:* c.559+1G>C			
RJ3	10.00	No	–58							
RJ4	2.67	No	72							
RJ7	2.40	No	23					*RB1:* loss		
RJ9	8.67	No	–22				*TP53:* loss		Yes	
RJ10	2.40	No	35				*TP53:* p.P87fs			*AR:* p.W742L
RJ11	8.13	No	–73	*CDK12:* c.269+1G>T						
RJ12-1	11.13	No	–81							
RJ13	3.07	No	–68							
RJ14	4.80	No	26				*TP53:* p.R36X		Yes	
RJ15	9.53	No	–38			*gATM:* p.E277X				
RJ16	9.70	No	–87		*gBRCA2:* p.Y949fs					
RJ17	6.00	No	–43		*gBRCA2:* p.Q754fs					
RJ18	8.00	No	–26	*CDK12:* p.Q62X						
RJ100	12.00	No	–68							
RJ105-1	7.67	No	–46							*AR:* p.L72H
RJ107-1	13.00	No	–88							*AR:* p.W742L, *AR:* p.T878A
RJ107-2	13.00	No	–88							
RJ108-1	4.20	No	16							
RJ108-2	4.20	No	16	*CDK12:* p.T1463fs						*AR:* p.H875Y, *AR:* p.T878A
RJ111-1	2.93	No	46						Yes	
RJ112-1	8.00	No	–38	*CDK12:* p.Q57X						
RJ122	5.00	No	–23						Yes	*AR:* p.L72H
RJ136	1.00	Yes	112							
RJ137	1.00	Yes	126							*AR:* p.W742C, *AR:* p.T878A
RJ140	8.00	No	–8				*TP53:* p.I5fs			
RJ155	2.00	No	45						Yes	
RJ20	10.00	No	–42		*BRCA2:* p.L1768fs					
RJ23-1	8.23	No	–58							
RJ24	5.13	No	–23		*BRCA2:* p.N1973del					
RJ25	6.03	No	–28			*gATM:* p.R38H				
RJ26	9.63	No	–75		*BRCA2:* c.786-2A>T, *gBRCA2:* p.S2156fs					

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eTable 7. Genomic Alteration Status, PFS, and PSA Change Over 12 Weeks in 66 Patients With ctDNA Samples Collected Before Docetaxel Treatment (cont.)

Patient	PFS (mo)	Censored	PSA Change Over 12 wks (%)	*CDK12* Defect	*BRCA2* Defect	*ATM* Defect	*TP53* Defect	*RB1* Defect	*AR* Gain	*AR* Mutation
RJ29	10.47	No	–79							*AR:* p.T878A
RJ31	2.07	No	45	*CDK12:* p.V56fs						
RJ34	3.00	Yes	–59							
RJ36	6.00	No	–43							
RJ41	12.00	No	–68							
RJ58	4.00	Yes	–18							
RJ66	6.20	No	–17							
RJ67	10.00	No	–64							
RJ68	3.00	Yes	–38		*BRCA2:* p.V1862fs					
RJ78	9.00	No	–55		*BRCA2:* loss					
RJ79	11.00	No	–77							
RJ80	11.00	No	–84	*CDK12:* p.A411fs						
RJ85	8.40	Yes	–68							*AR:* p.W742L
RJ88	2.00	Yes	73				*TP53:* p.C135F		Yes	
RJ93	8.90	No	–81							
RJ97	7.60	No	–69							
SY1	18.00	No	–83							
SY2	6.00	No	–82		*BRCA2:* loss					
SY6	8.00	No	–68							
SY9	10.00	No	–72	*CDK12:* p.Q944X			*TP53:* p.G244V			
SY25	6.00	Yes	–14							
BYY4	5.70	Yes	–36	*CDK12:* c.2964-2A>G, *CDK12:* p.Q695X						
BYY13	1.00	Yes	221							*AR:* p.T878A
BYY19	3.00	No	112							
WY20	7.00	No	–71	*CDK12:* p.Q498fs						*AR:* p.W742L
WY21	1.00	No	324				*TP53:* p.D259H			
WY27	2.00	No	78							
XJ2	15.20	Yes	–90							*AR:* p.W742L, *AR:* p.W742C
XJ6	1.00	No	97	*CDK12:* p.N432fs, *CDK12:* p.P55fs						
XJ8	14.00	Yes	–67							
FY4	5.50	No	–67				*TP53:* p.L348fs		Yes	
ZR1	8.00	Yes	–84							
ZZ1	1.00	No	216							

Abbreviations: ctDNA, circulating tumor DNA; g, germline; PFS, progression-free survival; PSA, prostate-specific antigen.

eTable 8. Genomic Alteration Status, PFS, and PSA Change Over 12 Weeks in 16 Patients With cfDNA Samples Collected Before Platinum-Based Chemotherapy

Patient	PFS (mo)	Censored	PSA Change Over 12 wk (%)	Somatic DDR Gene Defect	Germline DDR Gene Defect
RJ6	3.9	No	137.1		
RJ15	13	No	–73		*ATM:* p.E277X
RJ16	11	No	–82.1		*BRCA2:* p.Y949fs
RJ17	12	No	–83.1		*BRCA2:* p.Q754fs
RJ26	14	No	–79.3	*BRCA2:* c.7806-2A>T, *RAD50:* c.886-1G>T	*BRCA2:* p.S2156fs
RJ30	14	Yes	–54.7		*PALB2:* p.S254fs
RJ32	1.6	No	210.4		
RJ33	1	No	339		
RJ36	2.1	No	85.5		
RJ66	3.4	No	60.9		
RJ76	1	No	53.8	*ERCC3:* loss	
RJ77	9	Yes	–51.8	*CDK12:* p.I792fs	
RJ112-2	4.7	No	–44.2	*CHEK2:* loss	
RJ114-1	2	No	65		
WY8	1.2	No	123.6		
XJ1	8	No	–67.2		

Blank cells indicate no defect.
Abbreviations: cfDNA, circulating free DNA; DDR, DNA damage repair; PFS, progression-free survival; PSA, prostate-specific antigen.

eTable 9. Genomic Alteration Status, PFS, and PSA Change Over 12 Weeks in 16 Patients With cfDNA Samples Collected Before Olaparib Treatment

Patient	PFS (mo)	Censored	PSA Change Over 12 wk (%)	Somatic DDR Gene Defect	Germline DDR Gene Defect
RJ55	1.5	No	100		
RJ57	0.5	No	228.6		
RJ62	16	No	–32	*BRCA2:* p.N1784fs	
RJ64	2.4	No	80		
RJ73	10	No	–78.1	*CDK12:* c.2419+1G>A	
RJ74	2.4	No	421	*ATM:* c.6807+1G>T	
RJ83	1.2	No	67.9	*CDK12:* p.Q602X, *CDK12:* p.Y362X	
RJ84	2	No	143.8		
RJ96	1.5	No	51.7		
RJ102	9	No	–18.8		
RJ103	13	No	–62.2		
RJ104-1	9	No	89.4	*CDK12:* p.V513fs	
RJ110-2	8	No	–83.5		
RJ113-2	3	No	57.5	*ATM:* p.E38X	
RJ114-2	1	No	27.4	*CDK12:* p.Y295fs, *CDK12:* p.Q612X	
WY10	3.73	No	–37.2	*ATM:* p.E2744X, *CDH1:* p.G49fs, *CDK12:* p.P673fs, *CDK12:* p.V896fs	
WY13	4.3	No	–98.9		*BRCA2:* p.Y1894X
WY16	1.27	No	–61.2		
WY19	0.8	No	–23.5		
WY4	2.8	No	–62.4		*RAD51C:* p.R319X
WY7	5.3	No	–54.6		*BRCA2:* p.I1859fs
FY5	11	Yes	–77.9	*ATM:* c.185+1G>C, *FANCA:* loss, *BRCA2:* loss	*MLH3:* p.D206fs

Blank cells indicate no defect.
Abbreviations: cfDNA, circulating free DNA; DDR, DNA damage repair; PFS, progression-free survival; PSA, prostate-specific antigen.