MR. DANIEL HYUCK-MIN KWON (Orcid ID : 0000-0002-0830-7918)

DR. JONATHAN CHOU (Orcid ID : 0000-0003-1258-0391)

DR. STEVEN M YIP (Orcid ID : 0000-0003-2802-6651)

DR. MELISSA A REIMERS (Orcid ID : 0000-0002-5167-3630)

DR. HALA T. BORNO (Orcid ID : 0000-0001-6106-038X)

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Differential treatments outcomes in *BRCA1/2*, *CDK12* and *ATM* mutated metastatic castration-resistant prostate cancer

Running title: DNA repair-mutated prostate ca. outcomes

Daniel H. Kwon MD[1], Jonathan Chou MD PhD[1], Steven M. Yip MD[2], Melissa A. Reimers MD[3], Li Zhang PhD[1,4], Francis Wright[1], BS Mallika S. Dhawan MD[1], Hala T. Borno MD[1], Arpita Desai MD[1], Rahul R. Aggarwal MD[1], Alexander W. Wyatt PhD[5,6], Eric J. Small MD[1], Ajjai S. Alva MBBS[7], Kim N. Chi MD[5,8], Felix Y. Feng MD[9], Vadim S. Koshkin MD[1]

[1]Division of Hematology/Oncology, Department of Medicine, University of California San Francisco; [2]Tom Baker Cancer Centre, University of Calgary; [3]Division of Oncology, Department of Medicine, Washington University St. Louis; [4]Department of Biostatistics and Epidemiology, University of California San Francisco; [5]Vancouver Prostate Centre; [6]Department of Urologic Sciences, University of British

Columbia; [7]Division of Hematology/Oncology, Department of Internal Medicine, University of Michigan Ann Arbor; [8]BC Cancer Agency; [9]Department of Radiation Oncology, University of California San Francisco.

Corresponding author

Vadim S. Koshkin
550 16th Street, 6th Floor, Box 3211, Office 6555
San Francisco, CA 94158
Phone: (415) 353-9279
Email: vadim.koshkin@ucsf.edu

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Author contributions

Daniel H. Kwon: conceptualization, data curation, formal analysis, methodology, writing-original draft, writing-review and editing. Jonathan Chou: data curation, writing-review and editing. Steven M. Yip: data curation, writing-review and editing. Melissa A. Reimers: data curation, writing-review and editing. Li Zhang: formal analysis, methodology, writing-review and editing. Francis Wright: data curation. Mallika S. Dhawan: resources, writing-review and editing. Hala T. Borno: resources, writing-review and editing. Arpita Desai: resources, writing-review and editing. Rahul R. Aggarwal: resources, writing-review and editing. Alexander W. Wyatt: writing-review and editing. Eric J. Small: resources, writing-review and

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Precis:

Patients with metastatic castration-resistant prostate cancer (mCRPC) and DNA damage repair mutations (DDRm) had clinical outcomes and responses to treatment that varied based on specific DDRm type. Patients with *CDK12* mutations had the lowest and BRCA1/2 the highest PSA50 response rates to first-line abiraterone; and patients with *ATM* mutations had the lowest and BRCA1/2 the highest PSA50 response rates to carboplatin-based chemotherapy.

Abstract

Background: DNA damage repair mutations (DDRm) are common in patients with metastatic castration-resistant prostate cancer (mCRPC). Optimal standard therapy in this population is not well described.
Methods: A multi-institutional, retrospective study of patients with mCRPC and DDRm was conducted. Patient data including systemic therapies and responses were collected. Fifty percent PSA decline (PSA50) and overall survival (OS) from treatment start were compared by mutation and treatment type. A multivariable Cox proportional hazards model for OS was created controlling for DDRm, first-line treatment received in mCRPC, and clinical factors.
Results: The most common DDRm observed among 149 men with mCRPC were BRCA1/2 (44%), *CDK12* (32%), and *ATM* (15%). The majority received first-line abiraterone (40%) or enzalutamide (30%). PSA50 rate with first-line abiraterone was lower in CDK12 (52%) than BRCA1/2 (89%) (P=0.02). After first-line abiraterone or enzalutamide, median OS was longest for second-line carboplatin-chemotherapy (38 months) compared to abiraterone or enzalutamide (33 months), docetaxel (17 months), or cabazitaxel (11 months) (P=0.02). PSA50 responses to carboplatin-based chemotherapy were higher in BRCA1/2 (79%) than ATM (14%) (P=0.02) and CDK12 (38%) (P=0.08). In multivariable analysis, neither specific DDRm type nor first-line treatment was associated with improved OS.

Conclusions: Responses to standard therapies were generally superior in patients with BRCA1/2 mutations and inferior in patients with *ATM* or *CDK12* mutations. DDRm type did not independently predict OS. After progression on first-line abiraterone or enzalutamide, carboplatin-based chemotherapy was associated with the longest OS. These findings may inform treatment discussions and clinical trial design, and require prospective validation.

Keywords: ATM, biomarkers, BRCA2, CDK12, DNA repair, prostate cancer

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Figures: 1

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Introduction

Germline and somatic DNA damage repair mutations (DDRm) are common in metastatic castration-resistant prostate cancer (mCRPC), with a prevalence of 8-25%.[1–8] DDRm may lead to DNA repair deficiencies through various pathways including mismatch repair (MMR) and homologous recombination,[9] and may confer synthetic lethality with poly ADP-ribose polymerase inhibitors (PARPi). Clinical trials have shown a radiographic progression-free survival and overall survival benefit with the use of PARPi in patients with DDRm in the mCRPC setting,[10–14] primarily in BRCA1/2-mutated carriers.[15] As a result, the National Comprehensive Cancer Network recommends that men with mCRPC undergo germline testing and metastatic biopsy to assess for DDRm.[16]

There is conflicting evidence about the association of DDRm type with clinical outcomes of standard systemic therapies in mCRPC, including androgen signaling inhibitors (ASI) abiraterone and enzalutamide and taxane chemotherapies docetaxel and cabazitaxel, likely due to cohort size and heterogeneity.[4–8,17–

[19] Platinum-based chemotherapy may potentially benefit patients with DDRm,[20] but it is unknown how efficacy varies by DDRm type. Furthermore, little is known about outcomes based on treatment sequencing.

As more patients with mCRPC are found to have DDRm through increased testing, it is important to address these evidence gaps to inform oncologists and patients of anticipated outcomes to standard therapies, assess for potential biomarkers, and inform design of future clinical trials. Herein, we report and compare clinical outcomes in a multi-center cohort of patients with mCRPC and DDRm based on therapy and DDRm type. These data expand on a previously reported dataset of patients with *CDK12* mutations,[19] and differ by comparing treatment outcomes by specific DDRm type and treatment line.

Patients and Methods

A pooled retrospective analysis of patients at the University of British Columbia (UBC), University of California, San Francisco (UCSF), and University of Michigan (UM) with mCRPC and DDRm identified via somatic, germline, or circulating DNA next-generation sequencing (NGS) was conducted.

Patients and data collection

Genomic, clinical, and demographic data were obtained from electronic medical records from January 1, 1988 to March 16, 2018 for UBC and UM; data cutoff for UCSF was July 22, 2019. At UBC, deep targeted sequencing of plasma cell-free DNA (cfDNA) was performed with a 72-gene panel.[19] At UCSF, NGS was performed with the UCSF500 Cancer Gene Panel for metastatic biopsies; FoundationOne for metastatic biopsies and circulating tumor DNA (ctDNA); Strata for prostatectomy specimens; and Color Genomics for germline mutations. At UM, the CLIA/CAP-approved MI-ONCOSEQ NGS program was used for analysis of metastatic biopsies. University of Washington patients sequenced at UM via Stand up to Cancer were included in the UM cohort. All sites obtained Institutional Review Board approval, and de-identified patient data were shared between institutions in a Health Insurance Portability and Accountability Act-compliant manner.

Only patients with the following pathogenic or likely pathogenic DDRm were included in the analysis: *ATM, ATR, BRCA1, BRCA2, BARD1, BRIP1, CDK12*, *CHEK2*, Fanconi Anemia genes, mismatch repair genes (*MSH1, MLH3, MSH2, MSH3, MSH6, PMS1, PMS2*), *NBN*, *PALB2*, *RAD51, RAD51B, RAD51C, RAD51D,* and

RAD54L. Patients were categorized into five DDRm mutation groups: BRCA1/2, ATM, CDK12, mismatch repair (MMR), and Other.

In addition to disease-related clinico-pathologic data, systemic therapy data initiated after onset of mCRPC (defined as ≥2 consecutively rising serum prostate-specific antigen (PSA) values and/or new radiographic metastases in the setting of suppressed testosterone levels), were obtained for patients with DDRm. For each systemic therapy, treatment line, PSA decline ≥50% from baseline (PSA50 response), time from treatment start to next treatment start (TNT), and overall survival (OS) from start of treatment were obtained. Concurrent taxane chemotherapy with carboplatin was categorized as carboplatin-based chemotherapy. Patients were followed until date of death or last follow-up.

Statistical methods

Clinical and demographic characteristics were summarized by mutation group in contingency tables. PSA50 response rates, TNT, and OS of systemic therapies received in the first and second-line mCRPC settings were compared by therapy type and by mutation group using Fisher's exact test, Wilcoxon rank sum test, and log rank test, respectively. A multivariable Cox proportional hazard model of OS was used to account for age, stage, and PSA at diagnosis; ethnicity; presence of visceral metastases at time of mCRPC or metastasis; type of first-line treatment received; and mutation group. P-value <0.05 was considered significant for statistical testing. No multiple testing adjustments were performed. Analyses were performed using statistical computing software R (https://www.r-project.org).

Results

Patient characteristics

We identified 149 patients with mCRPC and DDRm. These DDRm were 60 *BRCA2* (40%), 47 *CDK12* (32%), 23 *ATM* (15%), 5 *BRCA1* (3%), 5 MMR (3%), 4 *PALB2* (3%), and 1 each of *BRIP1*, *FANCA*, *FANCC*, *FANCG*, and *RAD51C.* Demographic and clinical characteristics are described in Table 1. Characteristics including presence of visceral metastases (N=17; 11% of overall cohort) and source of genomic testing (N=128; 86% treatment-emergent) did not vary by mutation group, aside from a lower age of diagnosis in the ATM group compared to other groups (P=0.02). Median follow-up from start of first mCRPC treatment was 22.2 months.

PSA50 response rates

Among 137 patients who received systemic therapy after mCRPC onset, the most common first-line treatments were abiraterone (N=59), enzalutamide (N=44), docetaxel (N=19), and carboplatin-based chemotherapy (N=5, Table 2). In the overall cohort, there was no difference in PSA50 rate by first-line treatment type (Table 2). Among 59 patients who received first-line abiraterone, those with BRCA1/2 mutations had a higher PSA50 rate of 89% (16/18) than those with *CDK12* mutations at 52% (11/21; P=0.02, Table 2). There was no difference in PSA50 rate for first-line enzalutamide in patients with BRCA1/2 mutations (55%, 6/11) vs *CDK12* mutations (64%, 9/14; P=0.70, Table 2)

Among 108 patients who received a second-line therapy after mCRPC onset, most received enzalutamide, abiraterone, or docetaxel (Table 2). Overall, second- versus first-line PSA50 rates were lower for abiraterone (29% 5/17, vs 70% 37/53; P<0.01) and enzalutamide (30% 9/30, vs 65% 24/37; P<0.01). Responses in this second-line setting did not vary by treatment type or by DDRm. When restricting the cohort to patients who received an ASI in the first-line setting, the second-line treatment PSA50 rate was highest in patients treated with carboplatin-based chemotherapy at 67% (4/6) compared to 13% (3/24) for enzalutamide following abiraterone and 0% (0/8) for abiraterone following enzalutamide (P=0.01 across therapies, Supplementary Table 1).

PSA50 rates in the overall cohort regardless of treatment line are summarized in Table 3. PSA50 rate to carboplatin-based chemotherapy differed by mutation type: higher in patients with BRCA1/2 mutations (79%, 11/14) than patients with *ATM* mutations (14%, 1/7; P=0.02) or *CDK12* mutations (38%, 3/8; P=0.08). The PSA50 rate for patients treated with docetaxel (46%, 23/50), olaparib (33%, 8/24), and pembrolizumab (33%, 6/18) did not vary by DDRm (Table 3).

Time to next treatment

No differences in TNT were observed based on treatment type or sequence in the overall cohort and within mutation groups (Supplementary Table 2 and Supplementary Figure 1). However, among patients

who received first-line enzalutamide, those with *ATM* mutations had a longer TNT than those with BRCA1/2 or *CDK12* mutations (16 months vs 4 and 8 months, respectively, P<0.01). Time to next treatment for systemic therapies regardless of order received are described in Supplementary Table 3.

Overall survival

In the overall cohort, there was no association between first-line treatment type and OS (Figure 1A). Among patients with BRCA1/2 mutations, median OS was longest in those who received abiraterone (33 months) versus docetaxel (23 months) or enzalutamide (16 months) (P=0.02, Figure 1B). Among patients with *ATM* mutations, median OS was longest in those who received enzalutamide (not reached) or abiraterone (12 months) versus docetaxel (10 months) (P=0.02, Figure 1C). In the multivariable model, there was no difference in OS based on first-line treatment type or DDRm type (Table 4). Only the presence of visceral metastases (HR for death 2.1, 95%CI 1.1-4.2, P=0.03) was independently associated with OS. Patients with MMR or other mutations were excluded from the model due to small sample size. Among 67 patients who received a second-line therapy following first-line ASI, those who received another ASI or carboplatin-based chemotherapy had a longer median OS (39 and 38 months, respectively) than those who received docetaxel (17 months) or cabazitaxel (11 months) (P<0.01 across therapies, Supplementary Figure 2).

Discussion

This multi-institutional, retrospective cohort of patients with mCRPC and DDRm highlights important differences in patient outcomes based on mutation type and treatment received. In the era of precision medicine where genomic findings are leveraged to develop tailored treatment plans, this analysis provides essential insights to inform clinical decision-making for patients with a lethal form of prostate cancer. In patients treated with first-line abiraterone, patients with *CDK12* mutations had lower PSA50 response rates compared to patients with BRCA1/2 mutations. Tumors with BRCA1/2 mutations were also more sensitive to carboplatin-based chemotherapy than tumors with *ATM* mutations. A multivariable model of overall survival did not reveal significant differences based on DDRm type or the type of first-line treatment received in mCRPC. Overall outcomes were worse to all therapies in the second versus first-line mCRPC setting, with highest response rates and longest survival observed for

second-line carboplatin-based chemotherapy compared to other standard therapies in the post-ASI setting.

CDK12 is a kinase that regulates transcription and genomic stability, and *CDK12* alterations are more prevalent in mCRPC (7%) than localized prostate cancer.[21] Our findings build on mounting evidence that *CDK12* mutations define an aggressive prostate cancer subtype with poor outcomes such as shorter time on first-line ASI, as we and others have shown.[19,22–24] Although Nguyen and colleagues recently reported that patients with *CDK12* mutations had similar time on first-line ASI as wildtype controls, our study, as well as those of Schweizer and Antonarakis, found similar PSA50 response rates to first-line ASI in these patients.[22–24] No prospective data exist for therapies given in the first-line mCRPC setting compared by specific DDRm type. Exploratory analyses in the phase III PROfound study found that median progression-free survival on second-line ASI was lowest in patients with *CDK12* mutations (2.2mo) compared to patients with BRCA1/2 (3.0mo) or *ATM* mutations (4.7mo).[25] The different PSA50 rates to abiraterone underscore the different genomic signatures identified in *CDK12* versus *BRCA2*-mutated tumors.[26–28] In particular, whole genome and transcriptome studies in patients with mCRPC following progression on an ASI have demonstrated that *CDK12* and *BRCA2* alterations are associated with distinct structural variations that modify key regulators of progression.[28,29] Unsupervised clustering analysis has demonstrated that *CDK12* mutations are highly associated with tandem duplications, and *BRCA2* inactivation with deletions.[29] These differences, as well as *CDK12*'s role in other cellular processes such as transcription regulation, may lead to differential sensitivity and/or resistance to ASIs.[30] For example, *CDK12* is known to activate transduction pathways involved in ASI resistance, such as the PI3K-AKT and WNT-β-catenin pathways.[30,31] It is unclear why a similar difference was not identified for first-line enzalutamide in our cohort.

Moreover, we found that outcomes to standard therapies differed between patients with BRCA1/2 and *ATM* mutations. Patients with *ATM* mutations had longer TNT for first-line enzalutamide than patients with BRCA1/2 mutations, and lower PSA50 response rates to carboplatin-based chemotherapy given at any time. Response rates and TNT for taxanes were similar in BRCA1/2 and *ATM*-mutant subgroups, reflecting the non-selectivity of microtubule-targeting agents. It is recognized that *ATM*-mutated tumors have a distinct genomic signature compared to BRCA1/2-mutated tumors, which may explain lower

response rates to PARPi,[21,32] and perhaps differential outcomes to AR-targeted therapies and chemotherapy as well. Though inactivation of *BRCA2* may predict sensitivity to platinum chemotherapy in mCRPC,[18,20] sensitivity in *ATM*-mutated patients may be limited.[18]

Not surprisingly, response rates and TNT were worse in the second-line versus first-line mCRPC setting. In particular, responses to the second ASI received upon progressing on first-line ASI were limited, similar to responses in unselected patients.[33] However, we found higher responses and longer OS with second-line carboplatin-based chemotherapy after first-line ASI compared to second-line ASI or taxanes. This may be explained by the fact that most patients receiving carboplatin-based chemotherapy had *BRCA2* mutations, a group particularly sensitive to platinum-based chemotherapy, suggesting this may be a viable second-line treatment option for this patient subgroup. Sample size precluded stratification by mutation type.

The multivariable model of OS from start of first-line treatment did not reveal any differences based on first-line treatment type or DDRm type. It is challenging to make definitive conclusions about OS from this model due to likely selection bias for particular treatments based on disease and patient factors and heterogeneity of subsequent therapies which were likely tailored to DDRm type.

The overall PSA50 response rate of 46% to docetaxel in this DDRm population is comparable to that of historical controls in an unselected mCRPC population, e.g. 45% in the first-line mCRPC setting and 40% in the post-enzalutamide setting.[34,35] Notably, the PSA50 response rate to pembrolizumab of 33% was higher than in the phase II KEYNOTE-199 trial (6%).[36] This may be due to our smaller sample size and inclusion of two patients with MMR mutations who responded to pembrolizumab. Further investigation of DDRm as a biomarker for checkpoint inhibitor response is warranted.

Limitations of the study include the retrospective nature of the study, small sample size of several subgroups limiting interpretation of negative results, and heterogeneous patient population and method of tissue collection. Strengths include the large number of patients with DDRm, the multi-center cohort, and the inclusion of somatic DDRm, as most studies of DDRm have focused on germline variants.

These aspects highlight the "real world" perspective offered by this study. Notably, PARPis olaparib and rucaparib have recently become standard options in mCRPC harboring DDRm post-ASI (and post-taxane for rucaparib). Our largely pre-PARPi findings may not apply to the post-PARPi setting. As ASIs are now standard-of-care in the castration-sensitive setting, ASI treatment outcomes based on specific DDRm type must also be investigated in the castration-sensitive setting.

In conclusion, DDRm type was associated with divergent responses to standard therapies in mCRPC. These differences could help inform oncologists' discussions of anticipated outcomes of standard therapies with patients with DDRm. Further functional and prospective DDRm biomarker studies are still needed, and our study also underscores the importance of reporting gene-level outcomes in clinical trials of DDRm when possible.

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Table 1. Baseline characteristics of patients with mCRPC and DDRm, N=149

Characteristic	Overall N=149	BRCA1/2 N=65	ATM N=23	CDK12 N=47	MMR N=5	Other[a] N=9
Age at diagnosis, years; median, range	63 [34,87]	61 [34,86]	54 [46,75]	66 [48,87]	63 [51,77]	61 [57,87]
Ethnicity						
White	101 (68%)	42 (65%)	12 (52%)	35 (75%)	5 (100%)	7 (78%)
Asian	12 (8%)	7 (11%)	2 (9%)	2 (4%)	0	1 (11%)
African-American	7 (5%)	1 (2%)	2 (9%)	3 (6%)	0	1 (11%)
Hispanic	2 (1%)	0	2 (9%)	0	0	0
Other	10 (7%)	2 (3%)	2 (9%)	6 (13%)	0	0
Missing	17 (11%)	13 (20%)	3 (13%)	1 (2%)	0	0
Stage at diagnosis						
Localized	66 (44%)	31 (48%)	14 (61%)	15 (32%)	1 (20%)	5 (56%)

Regional lymph nodes	18 (12%)	7 (11%)	1 (4%)	8 (17%)	1 (20%)	1 (11%)
Metastatic	63 (42%)	27 (42%)	8 (35%)	22 (47%)	3 (60%)	3 (33%)
Missing	2 (1%)	0	0	2 (4%)	0	0
Visceral disease at time of metastasis or CRPC						
Yes	17 (11%)	8 (12%)	3 (13%)	6 (13%)	0	0
No	123 (83%)	51 (79%)	20 (87%)	38 (81%)	5 (100%)	9 (100%)
Missing	9 (6%)	6 (9%)	0	3 (6%)	0	0
PSA at diagnosis, ng/mL; median, range	18 [2,5000]	18 [4,5000]	16 [4,143]	20 [2,1647]	14 [4,2000]	17 [8,687]
Gleason score at diagnosis						
<8	28 (19%)	17 (26%)	3 (13%)	5 (11%)	1 (20%)	2 (22%)
8+	108 (73%)	43 (66%)	16 (70%)	39 (83%)	3 (60%)	7 (78%)
Missing	13 (9%)	5 (8%)	4 (17%)	3 (6%)	1 (20%)	0
Definitive local therapy						
Surgery	45 (30%)	20 (31%)	7 (30%)	13 (28%)	0	5 (56%)
Radiation therapy	36 (24%)	18 (28%)	6 (26%)	8 (17%)	3 (60%)	1 (11%)
None	65 (44%)	27 (42%)	10 (44%)	23 (49%)	2 (40%)	3 (33%)
Missing	3 (2%)	0	0	3 (6%)	0	0
Source of tissue						
Prostate	20 (13%)	7 (11%)	6 (26%)	6 (13%)	1 (20%)	0
Lymph node	5 (3%)	2 (3%)	0	2 (4%)	0	1 (11%)
Blood (ctDNA or cfDNA)	64 (43%)	38 (59%)	11 (48%)	15 (32%)	0	0
Germline	8 (5%)	2 (3%)	3 (13%)	0	0	1 (11%)
Liver	7 (5%)	2 (3%)	1 (4%)	2 (4%)	1 (20%)	1 (11%)

Table 1 continued. Baseline characteristics of patients with mCRPC and DDRm, N=149

Bone	2 (1%)	0	1 (4%)	1 (2%)	0	0
Other soft tissue[b]	8 (5%)	5 (8%)	0	2 (4%)	1 (20%)	0
Unknown metastasis	34 (23%)	9 (14%)	1 (4%)	18 (38%)	2 (40%)	4 (44%)
Missing	1 (1%)	0	0	1 (2%)	0	2 (22%)
# Lines of therapy received in mCRPC setting						
0	5 (3%)	3 (5%)	0	1 (2%)	1 (20%)	0
1-2	67 (45%)	36 (55%)	8 (35%)	18 (38%)	1 (20%)	4 (44%)
3+	72 (48%)	24 (37%)	14 (61%)	27 (57%)	2 (40%)	5 (56%)
Missing	5 (3%)	2 (3%)	1 (4%)	1 (2%)	1 (20%)	0

[a]Other mutations: 4 *PALB2*, 1 *BRIP1*, 1 *FANCA*, 1 *FANCC*, 1 *FANCG*, 1 *RAD51C*.

[b]Other soft tissue: 2 bladder, 2 epidural, 1 lung, 1 pelvic mass, 1 skin, 1 testis.

Table 2. PSA50 response rates of treatments received in mCRPC in patients with DDRm, by order received and mutation group

First line in mCRPC setting N=137	**Treatment**[a]	**Any DDRm**	**Mutation group**					**P-value** (Pairwise)		
			BRCA1/2 N=39	**ATM** N=20	**CDK12** N=39	**MMR** N=3	**Other** N=8	BRCA v ATM	BRCA v CDK12	ATM v CDK12
	Abiraterone N=59	70% 37/53	89% 16/18	86% 6/7	52% 11/21	100% 3/3	25% 1/4	1.00	**0.02**	0.19
	Enzalutamide N=44	65% 24/37	55% 6/11	75% 9/12	64% 9/14	-	-	0.40	0.70	0.68
	Docetaxel N=19	57% 8/14	86% 6/7	0 0/1	0 0/3	-	67% 2/3	n/a[c]	n/a[c]	n/a[c]
	Carboplatin-based N=5	40% 2/5	33% 1/3	-	0 0/1	-	100% 1/1	n/a[c]	n/a[c]	n/a[c]
	P-value[b]	0.50	0.06	0.33	0.18	n/a[c]	n/a[c]			

Second line in mCRPC setting N=108	Treatment[d]	Any DDRm	Mutation group					P-value (Pairwise)		
			BRCA1/2 N=38	ATM N=15	CDK12 N=13	MMR N=2	Other N=6	BRCA v ATM	BRCA v CDK12	ATM v CDK12
	Abiraterone N=27	29% 5/17	30% 3/10	0 0/4	-	-	67% 2/3	0.51	n/a[c]	n/a[c]
	Enzalutamide N=31	30% 9/30	42% 5/12	0 0/3	8% 1/12	100% 1/1	100% 2/2	n/a[c]	0.16	n/a[c]
	Docetaxel N=21	33% 4/12	17% 1/6	40% 2/5	-	-	100% 1/1	0.55	n/a[c]	n/a[c]
	Carboplatin-based N=7	57% 4/7	100% 3/3	0 0/2	100% 1/1	0 0/1	-	n/a[c]	n/a[c]	n/a[c]
	Cabazitaxel N=8	33% 1/3	50% 1/2	0 0/1	-	-	-	n/a[c]	n/a[c]	n/a[c]
	Olaparib N=5	20% 1/5	20% 1/5	-	-	-	-	n/a[c]	n/a[c]	n/a[c]
	P-value[b]	0.44	0.22	n/a[c]	n/a[c]	n/a[c]	n/a[c]			

[a]Not shown: 8 sipuleucel-T, 1 olaparib, 1 itraconazole.

[b]Comparison of PSA50 rates by treatment.

[c]Sample size too small for statistical testing.

[d]Not shown: 6 sipuleucel-T, 4 pembrolizumab, 2 clinical trial, 1 Radium-223, 1 other checkpoint inhibitor.

Table 3. PSA50 response rates of treatments received in mCRPC in patients with DDRm, regardless of treatment line

Treatment[a]	Any DDRm	Mutation group					P-value (Pairwise)		
		BRCA1/2	ATM	CDK12	MMR	Other	BRCA v ATM	BRCA v CDK12	ATM v CDK12
Abiraterone N=93	56% 47/84	65% 20/31	55% 6/11	47% 15/32	100% 3/3	43% 3/7	0.72	0.21	0.74
Enzalutamide N=93	39% 36/92	45% 15/33	64% 9/14	39% 12/31	0 0/1	0 0/13	0.34	0.62	0.20
Docetaxel	46%	61%	33%	33%	-	60%	0.24	0.18	1.00

N=58	23/50	11/18	3/9	6/18		3/5			
Carboplatin-based N=34	55% 18/33	79% 11/14	14% 1/7	38% 3/8	0 0/1	100% 3/3	**0.02**	0.08	0.57
Cabazitaxel N=30	22% 6/27	33% 2/6	50% 2/4	14% 2/14	-	0 0/3	n/a[c]	0.55	n/a[c]
Olaparib N=25	33% 8/24	50% 7/14	20% 1/5	0 0/3	-	0 0/2	0.34	n/a[c]	n/a[c]
Pembrolizumab N=19	33% 6/18	100% 1/1	33% 1/3	22% 2/9	100% 2/2	0 0/3	n/a[c]	n/a[c]	n/a[c]
Other checkpoint inhibitor[b] N=8	14% 1/7	0 0/2	0 0/2	33% 1/3	-	-	n/a[c]	n/a[c]	n/a[c]

[a]Not shown: 16 Sipuleucel-T, 11 Radium-223.

[b]1 ipilimumab/nivolumab, 7 unknown.

[c]Sample size too small for statistical testing.

Table 4. Multivariable model of overall survival from start of first-line mCRPC therapy in patients with DDRm.

	Hazard Ratio for Death	95% Confidence Interval	P-value
Age at diagnosis	1.01	0.98-1.05	0.55
Presence of visceral metastases	2.13	1.10-4.15	**0.03**
Metastases at diagnosis	1.51	0.80-2.86	0.20
PSA at diagnosis (log 10)	0.86	0.55-1.36	0.53
White ethnicity	1.11	0.55-2.23	0.76
First-line therapy			
Abiraterone	Reference		0.09
Enzalutamide	1.30	0.62-2.73	
Docetaxel	1.92	0.94-3.97	

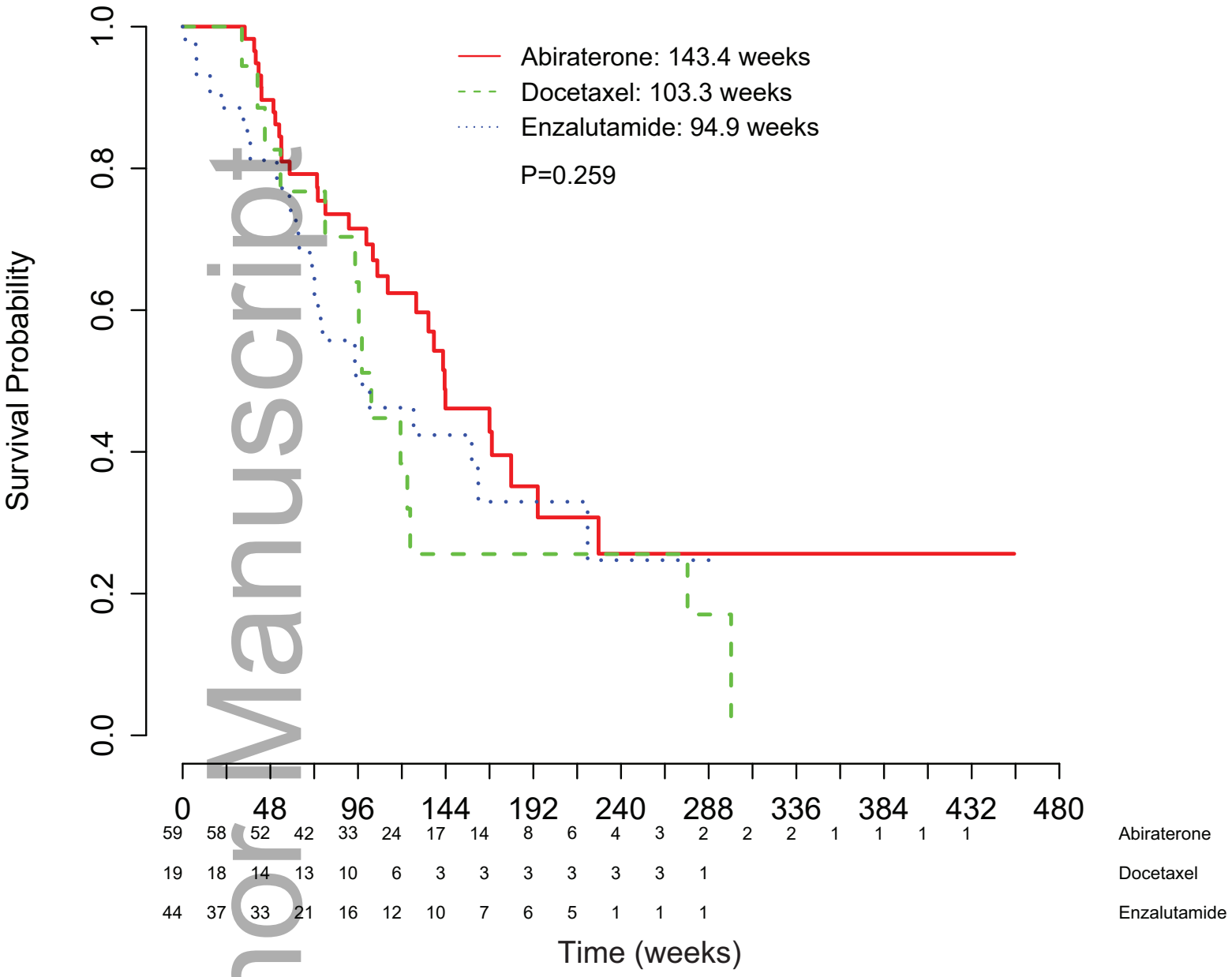
Carboplatin-based chemotherapy	3.40	0.70-16.6	
Other[a]	0.34	0.08-1.46	
Mutation[b]			
BRCA1/2	Reference		0.97
ATM	0.88	0.33-2.35	
CDK12	0.98	0.52-1.87	

[a]8 Sipuleucel-T, 1 olaparib, 1 cabazitaxel.

[b]MMR and other mutations not included due to small sample size.

Figure 1. Overall survival from start of first-line mCRPC therapy in patients with DDRm, by treatment type and DDRm

Analyses of overall survival from start of first-line therapy (abiraterone, enzalutamide, or docetaxel) in mCRPC as illustrated using Kaplan-Meier curves demonstrated A) Overall: no differences in survival by therapy type (P=0.26), B) BRCA1/2: longest survival in patients who received abiraterone (P=0.02), C) ATM: longest survival in patients with received enzalutamide (P=0.02), D) CDK12: no differences in survival. MMR and Other mutation groups not shown because of small sample size.



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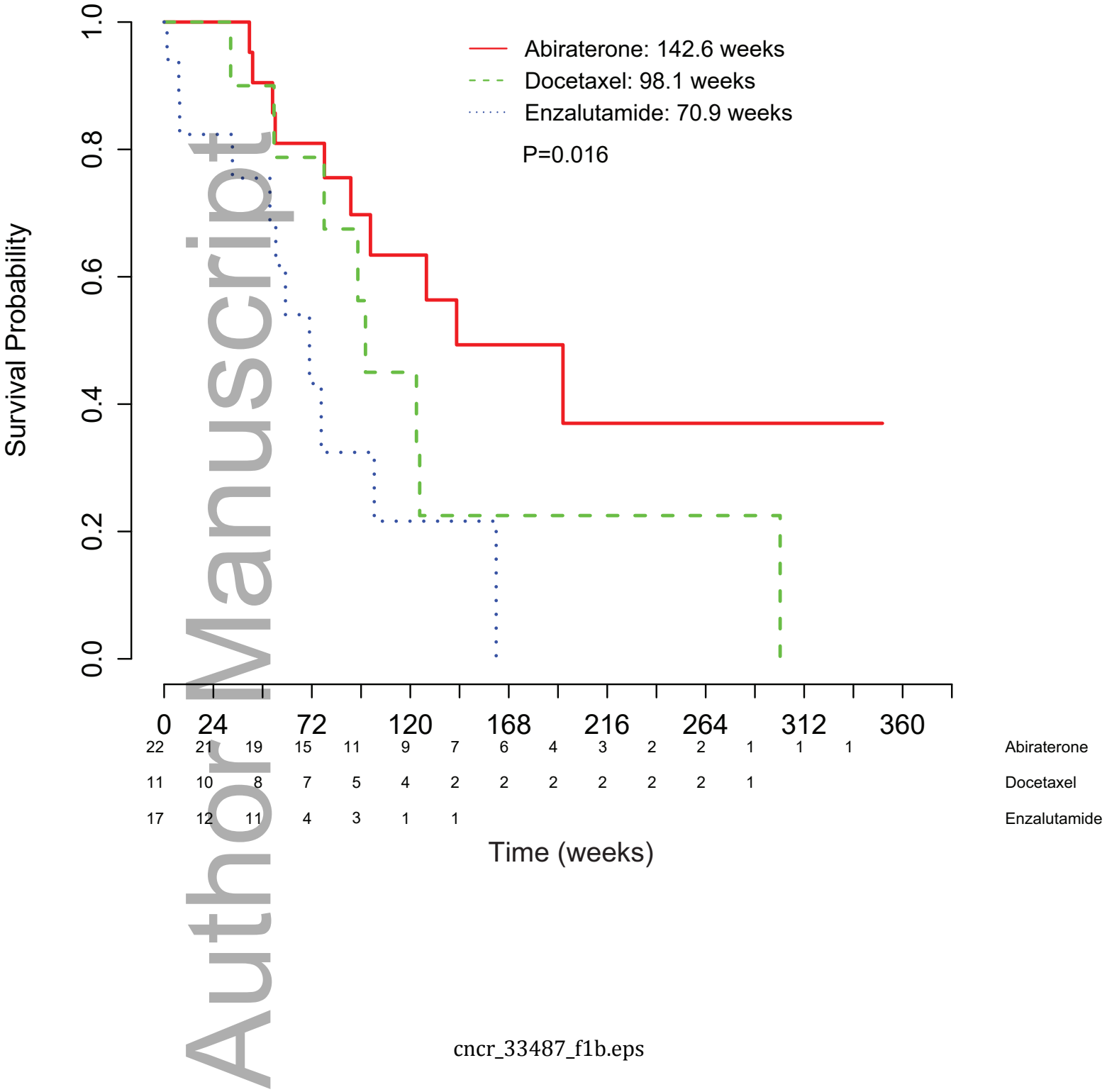
B. BRCA1/2, N=50



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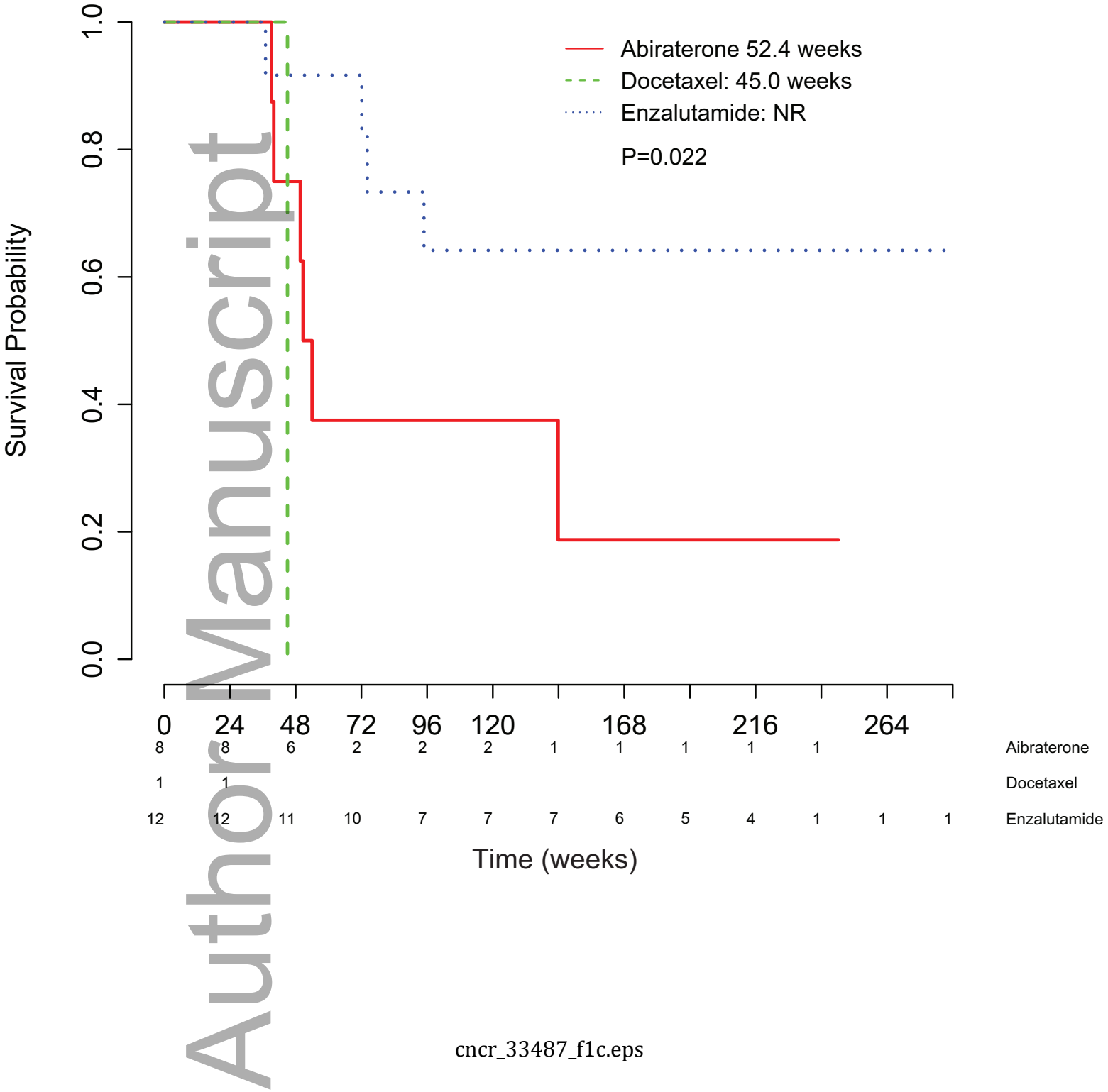
C. ATM, N=21



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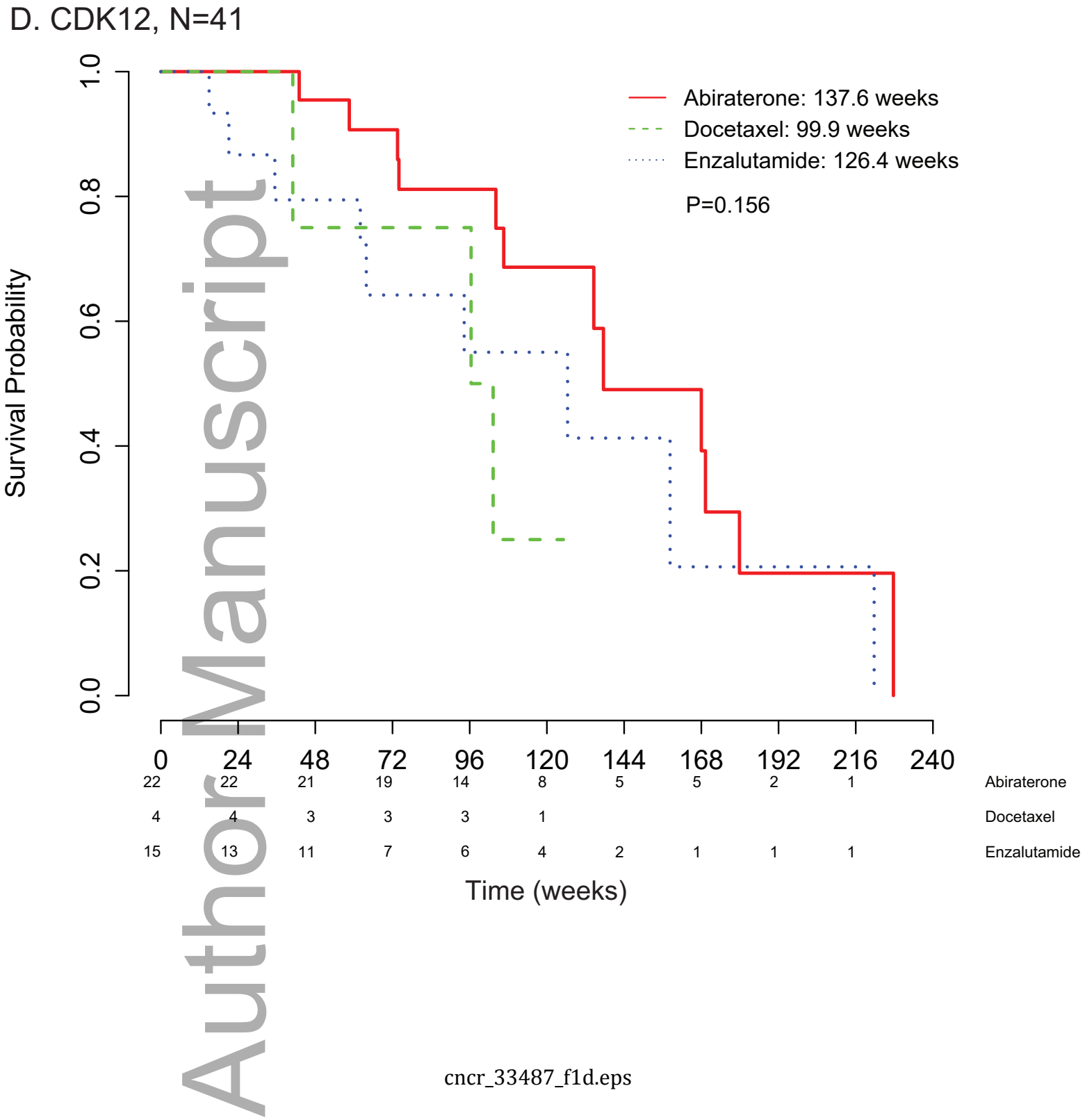

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