available at www.sciencedirect.com
journal homepage: www.europeanurology.com

European Association of Urology

Platinum Priority – Prostate Cancer

Editorial by Himisha Beltran and Alicia K. Morgans on pp. 48–49 of this issue

Predictive Genomic Biomarkers of Hormonal Therapy Versus Chemotherapy Benefit in Metastatic Castration-resistant Prostate Cancer

Ryon P. Graf[a,*], *Virginia Fisher*[a], *Joaquin Mateo*[b], *Ole V. Gjoerup*[a], *Russell W. Madison*[a], *Kira Raskina*[a], *Hanna Tukachinsky*[a], *James Creeden*[a], *Rachel Cunningham*[a], *Richard S.P. Huang*[a], *Douglas A. Mata*[a], *Jeffrey S. Ross*[a], *Geoffrey R. Oxnard*[a], *Jeffrey M. Venstrom*[a], *Amado J. Zurita*[c,*]

[a] *Foundation Medicine, Cambridge, MA, USA;* [b] *Vall d'Hebron Institute of Oncology (VHIO) and Vall d'Hebron University Hospital, Barcelona, Spain;* [c] *Department of Genitourinary Medical Oncology, The University of Texas MD Anderson Cancer Center, Houston, TX, USA*

Article info

Article history:
Accepted September 29, 2021

Associate Editor:
T Morgan

Statistical Editor:
Rodney Dunn

Keywords:
Prostate cancer
Predictive biomarkers
Real world
Propensity
Drug development

Abstract

Background: Biomarkers predicting second-generation novel hormonal therapy (NHT) benefit relative to taxanes are critical for optimized treatment decisions for metastatic castration-resistant prostate cancer (mCRPC) patients. These associations have not been reported simultaneously for common mCRPC genomic biomarkers.

Objective: To evaluate predictive associations of common genomic aberrations in mCRPC using an established comprehensive genomic profiling (CGP) system.

Design, setting, and participants: A retrospective cohort study used data from a deidentified US-based clinicogenomic database comprising patients treated in routine clinical practice between 2011 and 2020, evaluated with Foundation Medicine CGP in tissue biopsies obtained around the time of treatment decision. The main cohort included 180 NHT and 179 taxane lines of therapy (LOTs) from 308 unique patients. The sequential cohort comprised a subset of the main cohort NHT LOTs immediately followed by taxane from 55 unique patients.

Outcome measurements and statistical analysis: Prostate-specific antigen (PSA) response, time to next treatment (TTNT), and overall survival (OS) were assessed. Main cohort analyses were adjusted for known treatment assignment biases via inverse probability of treatment weighting (IPTW) in treatment interaction models.

Results and limitations: In the main cohort, patients with AR amplification (ARamp) or PTEN aberrations (PTENalt) had worse relative PSA response on NHT versus taxanes compared with patients without. Patients with ARamp, PTENalt, or RB1 aberrations (RB1alt) also had worse relative TTNT and OS on NHT but not on taxanes. In multivariable models for TTNT and OS adjusted via IPTW, ARamp, PTENalt, and RB1alt were shown as poor prognostic factors overall and demonstrated significant treatment interactions, indicating reduced hazards of therapy switch and death on taxanes versus NHT. Consistent associations favoring increased benefit from subsequent taxane despite prior

* Corresponding authors. Foundation Medicine, Cambridge, MA, USA. Tel. +1-858-349-8564 (R.P. Graf). Department of Genitourinary Medical Oncology, The University of Texas MD Anderson Cancer Center, Houston, TX, USA (A.J. Zurita).
E-mail addresses: rgraf@foundationmedicine.com (R.P. Graf), azurita@mdanderson.org (A.J. Zurita).

https://doi.org/10.1016/j.eururo.2021.09.030

NHT treatment line were observed only for ARamp in the sequential cohort, in which very few patients had RB1alt for assessment.
Conclusions: ARamp status is a candidate biomarker to predict poor effectiveness of NHT relative to taxanes in mCRPC in scenarios where both options are considered.
Patient summary: Specific alterations in the DNA of tumors may assist in choosing between novel oral hormonal therapies and standard chemotherapy in advanced prostate cancer patients.

1. Introduction

Novel hormonal therapies (NHTs) such as abiraterone and enzalutamide and taxane-based chemotherapy are the most common systemic therapies used to treat metastatic castration-resistant prostate cancer (mCRPC) [1]. To date, the CARD study [2] is the only phase III trial to evaluate these drugs in a randomized fashion, in the post-NHT, post-docetaxel setting. The majority of mCRPC patients in contemporary, routine clinical practice in the USA do not reach this treatment setting [1], and proper sequencing of these agents, especially in earlier lines, remains an unmet need [3]. Treatment strategies are expected to evolve with the recent approval of pembrolizumab for patients with microsatellite instability and high tumor mutational burden (TMB), and PARP inhibitors for those with DNA damage repair alterations, which make use of comprehensive genomic profiling (CGP) to direct treatment. Drugs with additional mechanisms of action will likely be approved in the coming decade. However, NHTs are expected to remain the default or backbone treatment option for most patients in the foreseeable future and taxanes the preferred alternative, and thus molecular markers that inform therapy selection between NHT and taxanes will clearly be useful for patient counseling and clinical decision-making.

Prognostic markers can help assess disease severity and indirectly aid clinical decisions that prioritize therapy escalation. In contrast, predictive biomarkers can identify patients who are more likely to benefit from one drug class over another, providing clearer value to guide treatment choices. Distinguishing prognostic from predictive biomarkers requires an epidemiological framework in which biomarker associations from more than one drug class are assessed in tandem, along with specific statistical criteria including interaction tests [4]. To date, very few studies have explicitly evaluated these biomarker-interdependent relationships in mCRPC, and have been limited to the evaluations of *AR* amplification (*AR*amp) [5–7] and androgen receptor splice variant-7 (AR-V7) [8–11], utilizing circulating cell-free tumor DNA (ctDNA) or circulating tumor cell (CTC) assays. For mCRPC patients, a higher ctDNA fraction and a higher CTC count both are established as prognostic markers for poorer outcomes [12,13] that can overestimate effect sizes for resistance markers detected in liquid biopsy [14,15]. For these reasons, we sought to identify biomarkers from tissue-based CGP that might help physicians prioritize NHT versus taxane use for patients with metastatic prostate cancer.

Evaluating a routine clinical practice cohort, we employed two complementary approaches to account for imbalances and biases: propensity weighting, frequently utilized in observational data-heavy fields such as epidemiology, economics, and social sciences [16], and sequential treatment analysis, analogous to drug crossover efficacy assessments performed in clinical trials [17]. Owing to extent and consistency of prior liquid biopsy literature [14], we hypothesized that the detection of *AR*amp proximal to treatment start would be associated with reduced response, efficacy, and survival with NHT but not with taxanes.

2. Patients and methods

2.1. Design, setting, and participants

2.1.1. Retrospective cohort study

Patients were included from the nationwide (US-based) Flatiron Health (FH)-Foundation Medicine (FMI) deidentified clinicogenomic database comprising patients with mCRPC diagnosis, receiving care within the FH network between January 2011 and December 2020 and with FMI CGP results within the same date range. The deidentified data originated from approximately 280 US cancer clinics (~800 sites of care). Retrospective longitudinal clinical data were derived from electronic health record data, comprising patient-level structured and unstructured data, curated via technology-enabled abstraction of clinical notes and radiology/pathology reports, and were linked to CGP data by deidentified, deterministic matching [18].

2.1.2. Main analysis cohort

The main analysis cohort was defined as patients with a tumor biopsy collected around the time of treatment decision (within 180 d before or up to 30 d after) for the initiation of a new treatment line with NHT or taxanes in the mCRPC setting, then subjected to CGP (Fig. 1). We reasoned that any tumor tissue acquired by a treating physician within 180 d prior to treatment initiation would have been obtained in anticipation of the need for additional therapy under early signs of treatment failure and would be unlikely to be influenced heavily by clonal outgrowth. We also reasoned that any tissue acquired within 30 d after treatment initiation would be unlikely to reflect changes in genomic profile related to the therapy just started.

2.1.3. Sequential treatment cohort

The sequential treatment cohort was defined as the subset of patients in the main analysis cohort treated initially with an NHT, who also were treated with a taxane immediately after the NHT (Fig. 1).

In addition to line of therapy and prior treatment history, preclinical features for imbalance adjustment were considered if part of the prognostic nomogram generated from the PREVAIL study [19], and if at least one value was present for >80% of observations within 360 d prior to

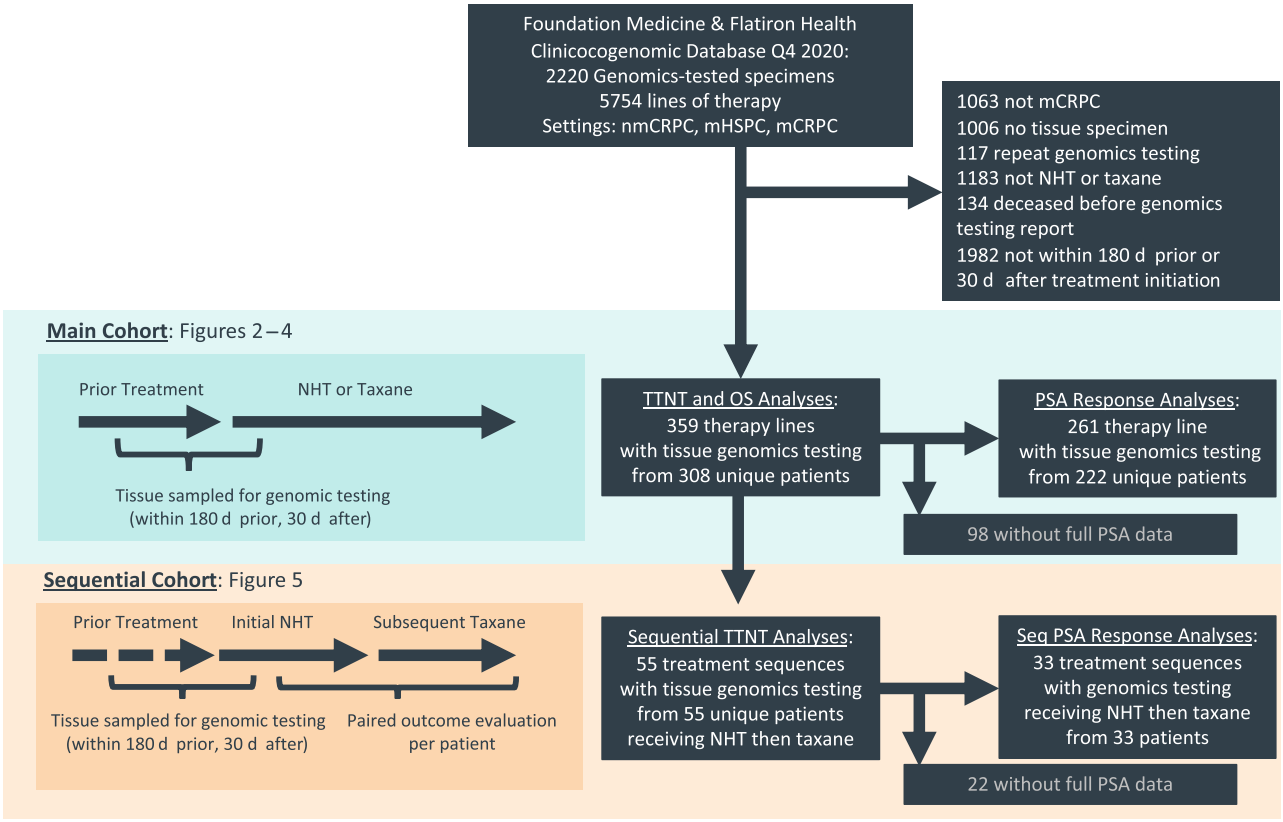

Fig. 1 – Cohort selection. Flowchart of cohort selection shown for main cohort and sequential cohort analyses. mCRPC = metastatic castration-resistant prostate cancer; mHSPC = metastatic hormone-sensitive prostate cancer; NHT = novel hormonal therapy; nmCRPC = nonmetastatic castration-resistant prostate cancer; OS = overall survival; PSA = prostate-specific antigen; TTNT = time to next treatment.

treatment initiation. Representativeness assessments made use of the aforementioned features. Approval for this study, including a waiver of informed consent and a HIPAA waiver of authorization, was obtained from the Western Institutional Review Board (protocol no. 20152817).

2.2. Comprehensive genomic profiling

A hybrid capture-based next-generation sequencing assay was performed on patient tumor biopsies in a Clinical Laboratory Improvement Amendments (CLIA)-certified, College of American Pathologists (CAP)-accredited laboratory (Foundation Medicine, Cambridge, MA, USA). FoundationOne or FoundationOne CDx assays interrogated all exons from minimum 324 cancer-related genes plus select introns from minimum 28 genes for rearrangement detection. Samples were evaluated for aberrations including base substitutions, insertions, deletions (short variants, denoted as sv), copy number alterations (amplifications and homozygous deletions, denoted as amp or del), and other select gene fusions/rearrangements, as described previously [20]. A minimum of six gene copies were required to call gene amplification. TMB was determined on up to 1.1 Mb of sequenced DNA [21].

2.3. General statistical considerations

The unit of measure in this study is lines of therapy (LOTs) on NHT or taxane. Individual patients could contribute multiple LOTs. Missing values were handled by simple imputation with the expected values conditional on observed covariates using random forests with the R package "missForest," and these imputed values were treated identically to measured values in a subsequent analysis. Time to next treatment (TTNT) was calculated from the initiation of treatment to the start of next treatment, or death if no subsequent treatments. The most recent treatment for patients without a recorded death was right censored to the date of last clinical visit or clinical record. Overall survival (OS) was calculated from the start of treatment to death from any cause, and patients without a recorded death were right censored to the date of last clinical visit or clinical record. Time-to-event analyses made use of Cox proportional hazard models. OS observations were left truncated to the date of CGP report if the latter was received after treatment initiation. To account for multiple observations per patient, all univariable or multivariable assessments of TTNT or OS made use of robust variances calculated by generalized estimating equations with a working independence structure. R version 3.6.3 software was used for all statistical analyses.

2.4. Hypotheses and secondary analyses

We hypothesized that *AR*amp detected proximal to treatment start would be associated with worse outcomes with NHT but not taxanes.

Including *AR*amp, prior relevant literature was utilized to preselect a set of gene alterations and pathways for analysis subjected to consistent and equal comparisons, and all results were reported in concordance with the guidelines of the American Statistical Association [22]. Multiple comparison adjustments were not performed; *p* values are reported to quantify the strength of association for each biomarker and outcome and not for null hypothesis significance testing, and biomarker analyses deliberately used an ensemble of outcomes (prostate-specific antigen [PSA] response, TTNT, OS, and interactions) and interpretations subsequently based upon the consistency of observations per biomarker, with no outcome measure standing on its own.

2.5. PSA response assessment

PSA response was evaluated by baseline-adjusted log linear regression models with biomarker-treatment interactions. A LOT was eligible for PSA response assessment if a PSA result was available within 60 d prior to the LOT, and a separate PSA result was available 1–180 d after. If multiple results were available, respective values most proximal to treatment initiation and 12 wk on treatment were used. Denoting the baseline as PSA_0 and on treatment as PSA_1, PSA responses were modeled as repeated measures with a log linear analysis of covariance model including biomarker status, treatment class, and their interaction:

$$\log_2(PSA_1) = \alpha + \beta_1 \log_2(PSA_0) + \beta_2 Treatment + \beta_3 Biomarker + \beta_4 Treatment * Biomarker + \epsilon$$

Resulting model output was then converted from log2 fold change to % PSA change.

2.6. Propensity score weighting

To adjust for imbalances in routine clinical practice treatment class assignment (Table 1), the inverse probability of treatment weighting (IPTW) technique was utilized in all models evaluating treatment class interactions with biomarkers in the main cohort [16]. Variables included the following: years from initial prostate cancer diagnosis to castration-resistant prostate cancer (CRPC), CRPC treatment line, baseline laboratory values (PSA, hemoglobin [HGB], alkaline phosphatase, albumin, and neutrophil:lymphocyte ratio [NLR]), Eastern Cooperative Oncology Group (ECOG) performance status score (categories: 0, 1, and 2+), site of biopsy (bladder, bone, liver, lymph node, prostate, and other), and whether the patient had prior NHT or taxane exposure at the time of treatment initiation. Propensity scores were generated using leave-one-out cross validation: for each treatment exposure, using the aforementioned features from all other treatment exposures, a random forest [23] algorithm predicted the probability (propensity) of the patient being assigned NHT or taxane. Individual treatments were subsequently weighted by the inverse of the propensity score; highly represented feature/treatment assignments are weighted less and rarer feature/treatment assignments are weighted more [16]. Standardized mean difference (SMD) was utilized to assess balance, and that within 10% was considered acceptable, 0% considered ideal [16].

2.7. Intrapatient sequential NHT and taxane comparisons

IPTW adjusts for known, quantifiable imbalances between patient populations. In order to better adjust potential unknown confounders, the PSA response and TTNT were compared between NHT and taxane treatment exposures within the same patients who received NHT followed by taxane, while acknowledging a disadvantage for the subsequent taxane. To account for multiple observations per patient, multivariable assessments of TTNT made use of robust variances calculated by generalized estimating equations with a working independence structure.

Table 1 – Characteristics of the main analysis cohort

Lines of therapy	NHT (N = 180)	Taxane (N = 179)
Age, median (Q1, Q3)	69.5 (65.0, 77.0)	70.0 (64.0, 76.5)
Years to CRPC, median (Q1, Q3)	1.7 (0.7, 6.2)	2.9 (1.1, 8.2)
Treatment line, n (%)		
1st	102 (57)	42 (24)
2nd	42 (23)	40 (22)
3rd	18 (10)	43 (24)
4th+	18 (10)	54 (30)
Practice type, n (%)		
Academic	20 (11)	8 (5)
Community	160 (89)	171 (96)
ECOG performance status, n (%)		
0	49 (39)	36 (25)
1	64 (50)	90 (62)
2+	14 (11)	20 (14)
Missing observations	53	33
PSA		
Median (Q1, Q3)	21.1 (6.7, 85.0)	77.2 (18.7, 186.1)
Missing observations	48	17
Hemoglobin		
Median (Q1, Q3)	11.5 (10.4, 12.8)	11.1 (9.8, 12.1)
Missing observations	29	7
Alkaline phosphatase		
Median (Q1, Q3)	99.0 (72.5, 170.5)	100.0 (78.0, 168.0)
Missing Observations	29	10
Albumin		
Median (Q1, Q3)	40.0 (37.0, 42.0)	39.0 (36.0, 42.0)
Missing observations	29	9
Neutrophil:lymphocyte ratio		
Median (Q1, Q3)	3.4 (2.3, 5.1)	5.0 (2.8, 8.1)
Missing Observations	57	30
Prior NHT, n (%)	57 (32)	131 (73)
Prior taxane, n (%)	49 (27)	73 (41)
Prior opioid, n (%)	73 (41)	86 (48)
Prior NHT (mHSPC setting), n (%)	4 (2)	1 (1)
Prior taxane (mHSPC setting), n (%)	16 (9)	15 (8)
Biopsy site, n (%)		
Bladder	13 (7)	18 (10)
Bone	24 (13)	31 (17)
Liver	22 (12)	52 (29)
Lymph node	37 (21)	32 (18)
Other	31 (17)	29 (16)
Prostate	53 (29)	17 (10)
Reached next therapy, n (%)	154 (86)	164 (92)
Median (Q1, Q3) months follow-up of censored	8.7 (3.6–15.8)	3.7 (2.1–6.6)
Deceased, n (%)	110 (61)	141 (79)
Median (Q1, Q3) months follow-up of censored	17.8 (9.1–29.8)	7.6 (3.5–15.2)

CRPC = castration-resistant prostate cancer; ECOG = Eastern Cooperative Oncology Group; mHSPC = metastatic hormone-sensitive prostate cancer; NHT = novel hormonal therapy; PSA = prostate-specific antigen.
Missing values are excluded from denominators; subsets may not add up to total at the top of column.

3. Results

3.1. Clinical characteristics of analysis cohort

Of the 359 LOTs eligible for inclusion, 180 were NHT treated and 179 were taxane treated. Overall, 220, 43, and two patients contributed one, two, or three LOTs, respectively. In all, 144 (40%), 82 (23%), 61 (17%), and 72 (20%) were first, second, third, and fourth LOTs, respectively. Compared with taxane use, NHT use was more frequent in earlier lines, and at the time of treatment initiation NHT-treated patients had lower PSA (median: 21.1 vs 77.2), higher HGB (median: 11.5 vs 11.1), lower NLR (median: 3.4 vs 5.0), less frequent prior NHT use (32% vs 73%), and reduced prior taxane use (27% vs 41%). Of the 359 LOTs, 318 (89%) had ended, with median follow-up of censored being 5.6 mo, and 251 (70%) were associated with a death event, with median follow-up of censored being 13.7 mo. Results are summarized in Table 1.

The characteristics of the main cohort in the entire database (having a biopsy within 180 d prior to or 30 d after treatment initiation) were similar to those of the

NHT and taxane LOTs in the entire database, including prior treatment lines, PSA levels, ECOG, and other features considered. The subset of the main analysis cohort representing the sequential analysis cohort was similarly comparable. The subset without evaluable PSA response data was also broadly reflective of the main analysis cohort, with the notable exceptions of missing data for pretreatment laboratory measures such as PSA, HGB, albumin, and alkaline phosphatase (Supplementary Tables 1–3). Of the 359 LOTs, 259 were initiated before the CGP report was released to the clinician, leaving 100 treatment decisions as potentially influenced by genomics (Supplementary Table 4). Of these, only *TP53* aberrations differed significantly by treatment assignment, with patients testing positive more likely to receive NHT than taxane ($p < 0.001$).

3.2. Genomic characteristics of the analysis cohort

The absolute and relative frequency of genomic aberrations observed in the main analysis cohort (Fig. 2A) is similar to previously published mCRPC cohorts of larger size [24]. Subsequent analyses make use of combined gene signatures (Fig. 2B).

3.3. Inverse probability of treatment weighting

Before weights were applied, 17 of 23 disease- and treatment-related clinical features (Supplementary Fig. 1C) were >10% SMD. After applying IPTW, three of 23 clinical features were >10% SMD (Supplementary Fig. 1D). Unadjusted for IPTW, worse TTNT (hazard ratio [HR]: 1.77, 95% confidence interval [CI]: 1.41–2.22, $p < 0.0001$) and OS (HR: 1.72, 95% CI: 1.33–2.21, $p < 0.0001$) were observed for taxanes versus NHT. Adjusted for IPTW, the difference between taxane and NHT was reduced for TTNT (HR: 1.30, 95% CI: 1.02–1.66, $p = 0.033$) and OS (HR: 1.24, 95% CI: 0.90–1.63, $p = 0.18$).

3.4. Univariable outcomes and single gene by gene treatment interactions

Associations of PSA response, TTNT, and OS from the most proximal NHT or taxane treatment separately, or as interactions with IPTW applied, are shown graphically (Fig. 3A–I) and numerically (Supplementary Tables 5–7) per biomarker.

*AR*amp was observed in 30% of the tumor specimens, with increasing prevalence from the first (17%) to the fourth (44%) LOT. Patients receiving NHT had worse PSA response with *AR*amp versus those not receiving it, with a PSA change of 158% higher than those testing negative (95% CI: 50.2–345%, $p = 0.0006$), but *AR*amp(+) made no difference in PSA response in those treated with taxane-based chemotherapy (% change: 5.3, 95% CI: −35.1% to 71.0%, $p = 0.83$). *AR*amp was additionally associated with a greater risk of treatment change (TTNT HR: 2.03, 95% CI: 1.33–3.08, $p < 0.001$) and death (OS HR: 2.28, 95% CI: 1.45–3.59, $p < 0.001$) for NHT, but not for patients on taxanes (TTNT HR: 1.05, 95% CI: 0.76–1.46, $p = 0.8$; OS HR: 1.03, 95% CI: 0.70–1.51, $p = 0.9$). While additionally balancing for known NHT versus taxane treatment assignment imbalances with IPTW, *AR*amp status demonstrated treatment interactions, indicating that on average *AR*amp(+) patients had a better PSA decline on taxanes relative to NHT (% change: −59.3%, 95% CI: −80.4% to −15.4%, $p = 0.016$), as well as a lower rate of therapy change (TTNT HR: 0.50, 95% CI: 0.30–0.84, $p = 0.009$) and a lower risk of death (OS HR: 0.51, 95% CI: 0.29–0.89, $p = 0.017$).

A diverse literature exists describing many types of *AR* short variant mutations with varying degrees of anticipated resistance to different NHTs based on in vitro studies [25]. Prior evaluations have yielded inconsistent associations with clinical outcomes [13,26]. While the overall prevalence of these alterations was lower than *AR*amp (Supplementary Table 8) and further stratification would reduce the power to detect outcome associations, we nonetheless sought to test whether specific point mutations might have associations

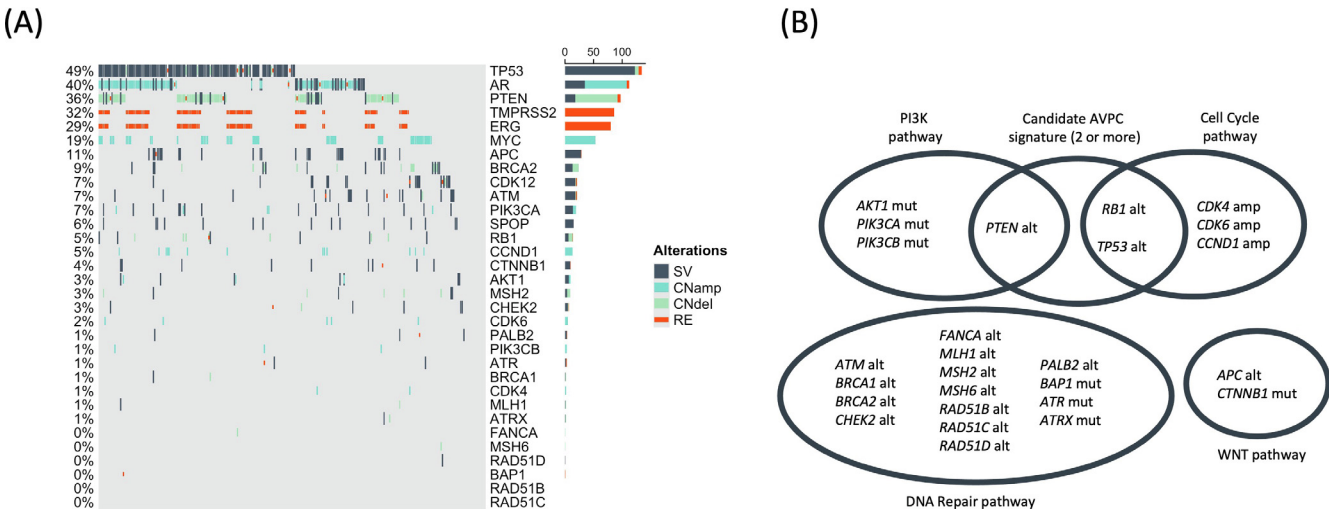

Fig. 2 – Genomic landscape of cohort: (A) oncoprint showing relationship between aberrations from all samples of patients evaluated in the cohort and (B) Venn diagrams showing the relationships between multigene signatures and pathways.

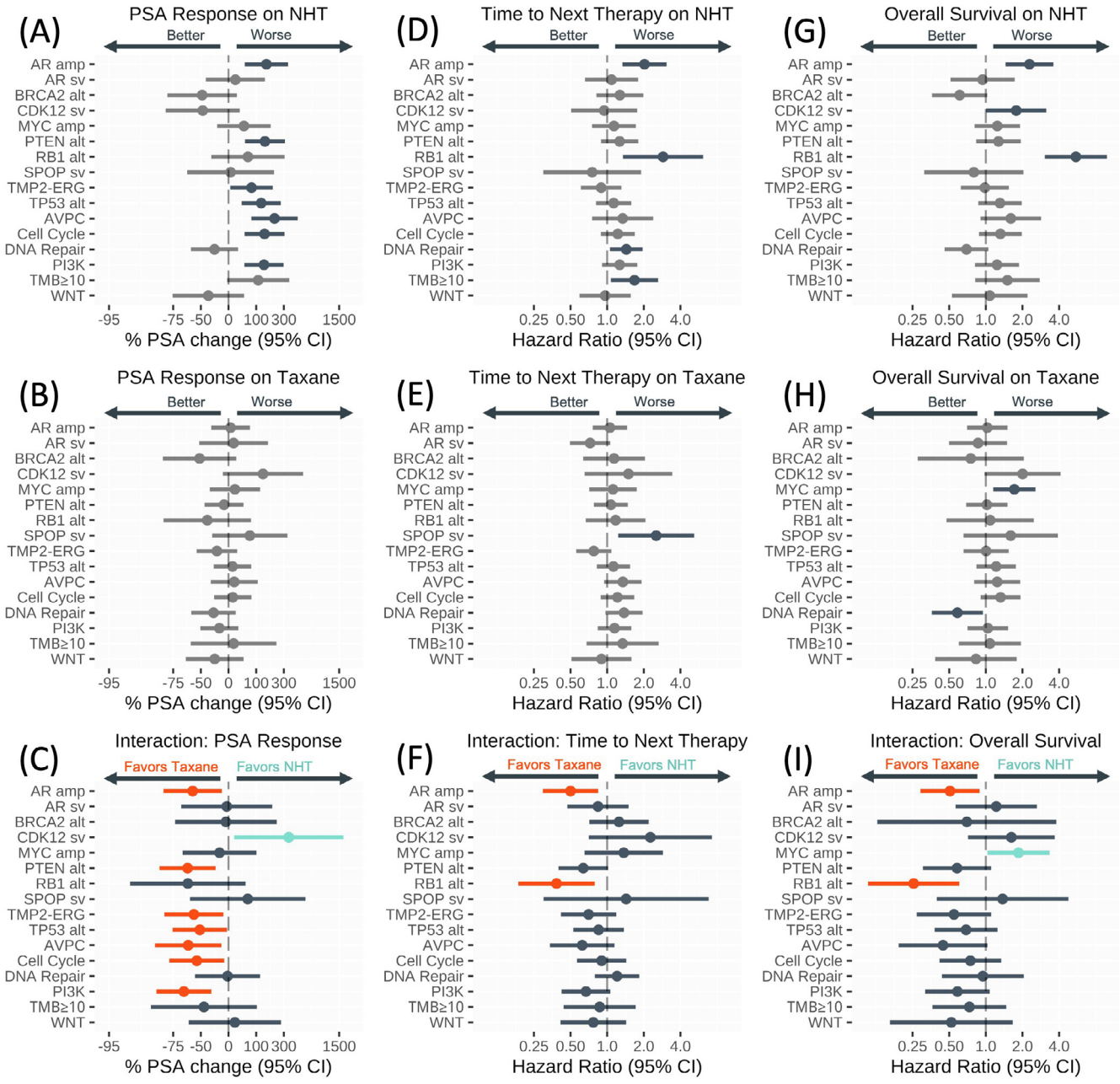

Fig. 3 – Main cohort single biomarker interaction models. The point estimates and 95% confidence intervals of Cox models are shown with forest plots. The log fold PSA change from pretreatment to on treatment was compared between patients testing positive and those testing negative for the indicated biomarker for (A) NHT, (B) taxane, and (C) interactions. Time to next therapy is compared between patients testing positive and those testing negative for the indicated biomarker for (D) NHT, (E) taxane, and (F) interactions. Overall survival is compared between patients testing positive and those testing negative for the indicated biomarker for (G) NHT, (H) taxane, and (I) interactions. For therapy interaction tests, the point estimate and confidence intervals represent the relative treatment class-specific outcome estimates for patients testing positive for the indicated biomarker on taxanes versus NHT. Numerical results represented graphically here can be found in Supplementary Tables 5–7. alt = deletions or known inactivating short variant mutations; amp = amplifications; AVPC = AVPC signature; Cell cycle = cell cycle alterations; CI = confidence interval; DNA repair = DNA repair alterations; NHT = novel hormonal therapy; PI3K = PI3K pathway alterations; PSA = prostate-specific antigen; sv = known functional short variant mutations; TMP2-ERG = TMPRSS2-ERG fusion; WNT = WNT pathway alterations.

that are diluted by combining the most common previously described mutations (Supplementary Table 9). In multivariable models containing *AR*amp, T878A was associated with reduced TTNT on NHT (HR: 2.14, 95% CI: 1.04–4.48, $p = 0.038$) but not OS, and H875Y was associated with reduced OS on NHT (HR: 2.80, 95% CI: 1.27–6.17, $p = 0.011$) but not TTNT.

RB1 mutations and deletions (*RB1* aberrations [*RB1*alt]) were present in 5.0% of samples, and had strong associations with worse TTNT (HR: 2.88, 95% CI: 1.35–6.14, $p = 0.006$) and OS (HR: 5.49, 95% CI: 3.05–9.89, $p < 0.001$) compared with *RB1*wt for patients receiving NHT but not for patients receiving taxanes (TTNT on taxanes, HR: 1.17, 95% CI: 0.67–2.06, $p = 0.6$; OS for patients on taxanes, HR:

1.09, 95% CI: 0.48–2.48, p = 0.8), and significant IPTW-adjusted treatment interactions suggesting better TTNT (HR: 0.38, 95% CI: 0.19–0.79, p = 0.009) and OS (HR: 0.26, 95% CI: 0.11–0.60, p = 0.002) for those with *RB1*alt treated with taxanes relative to NHT.

Other alterations with notable interactions in our cohort included *MYC* amplifications (*MYC*amp) and *PTEN* short variant mutations and deletions (*PTEN* aberrations [*PTEN*alt]), with respective prevalence of 19% and 35%. However, the magnitudes of the associations were lower than for *AR*amp and *RB1*alt; patients with *MYC*amp had worse OS on taxanes versus those on NHT (HR: 1.86, 95% CI: 1.03–3.34, p = 0.039), although the IPTW-adjusted TTNT interaction was directionally consistent but not as strong (HR: 1.37, 95% CI: 0.65–2.87, p = 0.4). *PTEN*alt had associations for better relative PSA response (% change: −64.2%, 95% CI: −82.2% to −27.7%, p = 0.004), TTNT (HR: 0.65, 95% CI: 0.40–1.02, p = 0.058), and OS (HR: 0.58, 95% CI: 0.30–1.11, p = 0.098) on taxanes versus NHT.

CDK12 short variants (*CDK12*sv), while present in only 6.1% of the cohort, had directionally worse OS on NHT (HR: 1.79, 95% CI: 1.01–3.14, p = 0.048) and taxanes (HR: 2.0, 95% CI: 0.98–4.12, p = 0.058). *SPOP* short variants (*SPOP*sv) had an association with worse TTNT on taxanes (HR: 2.43, 95% CI: 1.23–5.19, p = 0.012) without other notable associations. Several other biomarkers (*TP53*alt, *TMPRSS2-ERG,* aggressive variant prostate cancer [AVPC] signature, cell cycle alterations, DNA repair alterations, and PI3K pathway alterations) had IPTW-adjusted treatment interactions indicating more favorable PSA response on taxanes versus NHT, but without a similar magnitude of associations seen for TTNT and OS. We did not identify clear prognostic or predictive associations for *BRCA2*alt.

Sensitivity analyses were performed by further stratifying interaction models by LOTs, restricting to only first and second line exposures, or excluding specimens obtained after treatment start date (Supplementary Fig. 2–4). Outcome associations were largely insensitive to alternate contexts, with similar point estimates and slightly broader CIs.

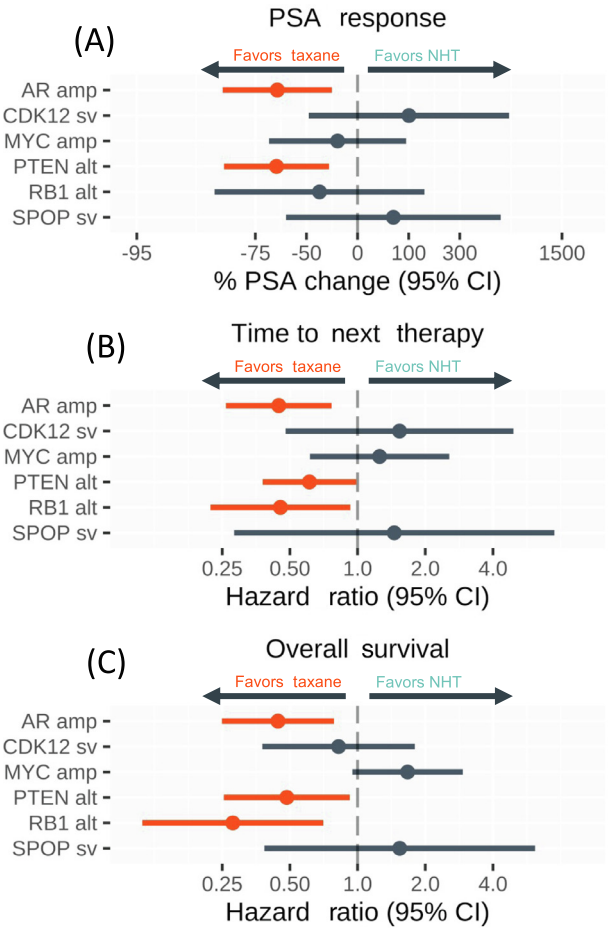

Fig. 4 – Main cohort multivariable treatment interaction models. Genomic aberrations were assessed for additive and independent prognostic and predictive value with respect to (A) PSA response, (B) TTNT, and (C) OS. Forest plots represent the interaction terms from multivariable models, with numerical values from full models in Supplementary Table 10. alt = deletions or known inactivating short variant mutations; amp = amplifications; CI = confidence interval; NHT = novel hormonal therapy; OS = overall survival; PSA = prostate-specific antigen; sv = known functional short variant mutations; TTNT = time to next treatment.

3.5. Multivariable treatment interactions

As the presentation of *AR*amp, *CDK12*sv, *MYC*amp, *PTEN*alt, *RB1*alt, and *SPOP*sv had overlaps (Fig. 2A), we sought to evaluate the independent prognostic and predictive contributions of these markers in multivariable models for TTNT and OS, adjusted for treatment class imbalances via IPTW. A combination of the biomarkers yielded results consistent with interaction models per biomarker, with *AR*amp, *PTEN*alt, and *RB1*alt all being poor prognostic factors overall, and demonstrating significant treatment interactions indicating reduced hazards of TTNT and OS on taxanes versus NHT (Fig. 4). The interaction of *MYC*amp and taxane versus NHT with OS was reduced (HR: 1.67, 95% CI: 0.95–2.94, p = 0.076) compared with single-interaction models, while *CDK12*sv was without strong interactions (HR: 0.82, 95% CI: 0.38–1.80, p = 0.6). Numerical values for Fig. 4 graphical representations and additional multivariable results can be found in Supplementary Table 10.

Sensitivity analyses were performed by further stratifying interaction models by LOTs, restricting to only first and second line exposures, or excluding specimens obtained after treatment start date (Supplementary Fig. 5–7). Outcome associations remained largely insensitive to alternate contexts, with similar point estimates and slightly broader CIs.

3.6. Intrapatient NHT to taxane crossover

An alternate method for adjusting for imbalances between patients is to compare the effects of drug classes on the same patient, acknowledging that the second treatment would be at a disadvantage. Fifty-five patients who received NHT from the previous analyses were subsequently treated with taxane immediately after NHT. Of these, 33 (60%) had PSA responses evaluable for both treatments (Fig. 1).

In this analysis, *AR*amp had the most consistent treatment class–specific outcome associations. Patients with *AR*amp detection proximal to initial NHT had better relative

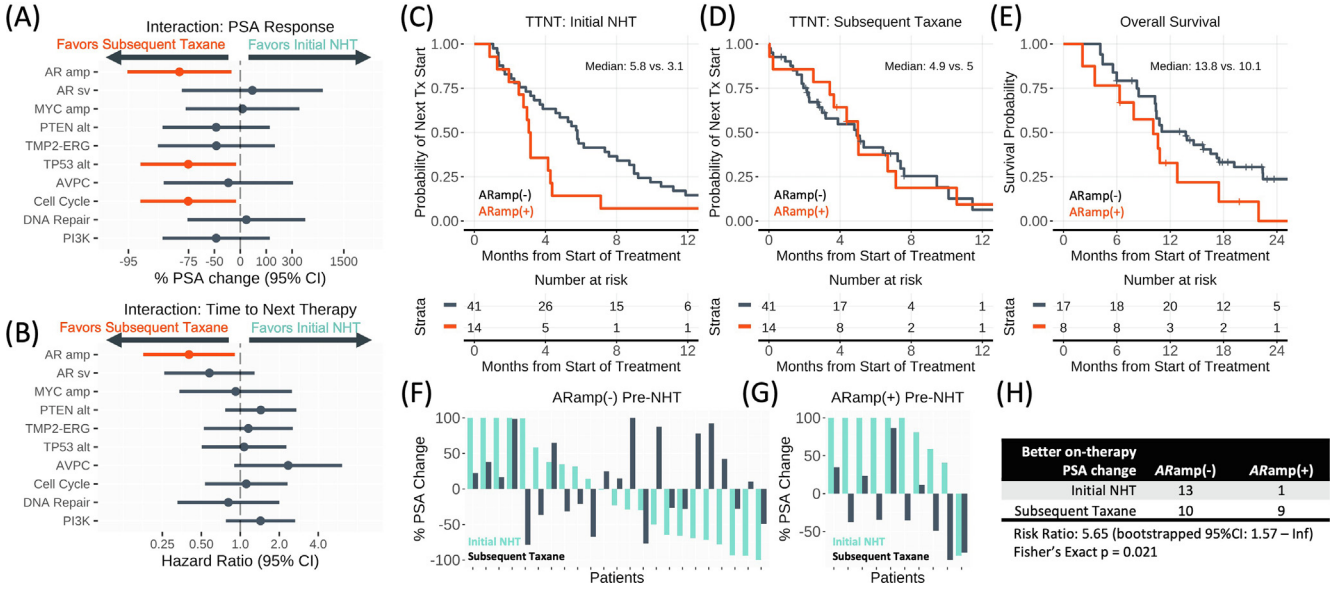

Fig. 5 – Intrapatient crossover evaluation of NHT followed by taxane. Patients who received NHT proximal to tissue biopsy subsequently received taxane. Point estimates and 95% confidence intervals of interaction terms from Cox models per biomarker are shown with forest plots for (A) PSA response and (B) time to next therapy. Only biomarkers with five or more patients testing positive are shown graphically, evaluating outcomes associated with *AR* amplifications, Kaplan-Meier plots of TTNT for the (C) initial NHT, (D) subsequent taxane, and (E) subsequent OS of this group of patients, indexed from the start of NHT (left truncated for those for whom the report date was after the index date). Waterfall plots show paired PSA change per patient for initial NHT and subsequent taxane, for patients (F) negative and (G) positive for *AR* amplifications prior to initial NHT. Increases of >100% were capped at 100% for graphical representation. (H) Comparison of Fig. 5F and 5G. Patients had better on-therapy PSA change on taxane if the PSA decrease was greater on the taxane versus the prior NHT, or less of an increase on the taxane versus initial NHT; otherwise, they had better on-therapy PSA change on the initial NHT. Numerical results represented graphically here can be found in Supplementary Tables 11 and 12. alt = deletions or known inactivating short variant mutations; amp = amplifications; AVPC = AVPC signature; Cell cycle = cell cycle alterations; CI = confidence interval; DNA repair = DNA repair alterations; NHT = novel hormonal therapy; OS = overall survival; PI3K = PI3K pathway alterations; PSA = prostate-specific antigen; sv = known functional short variant mutations; TMP2-ERG = TMPRSS2-ERG fusion; TTNT = time to next treatment; Tx = treatment.

PSA response (% change: −80.4%, 95% CI: −95.1% to −21.0%, $p = 0.023$) and TTNT (HR: 0.40, 95% CI: 0.18–0.91, $p = 0.028$) on the subsequent taxane (Fig. 5A and B). Of note, in this context, comparable associations for *PTEN*alt were not seen for TTNT interactions (HR: 1.44, 95% CI: 0.76–2.71, $p = 0.3$) or PSA response (% change: −47.6%, 95% CI: −87.5% to 121%, $p = 0.4$), the same holding true for *MYC*amp as well as for TTNT (HR: 0.92, 95% CI: 0.34–2.51, $p = 0.9$) and PSA response (% change: 6.2%, 95% CI: −76.8% to 387%, $p = 0.9$). The very small absolute numbers of positive patients for other alterations (*BRCA2*alt, *CDK12*sv, *RB1*alt, *SPOP*sv, TMB10, and WNT pathway alterations) limits the ability to interpret these further.

*AR*amp detection versus nondetection was associated with reduced TTNT on the initial NHT (HR: 2.25, 95% CI: 1.19–4.27, $p = 0.013$) without any observed difference in subsequent taxane effectiveness (HR: 0.92, 95% CI: 0.45–1.85, $p = 0.8$), and with reduced OS (HR: 2.21, 95% CI: 1.02–4.78, $p = 0.044$) from the start of NHT (Fig. 5C–E).

Further evaluating PSA responses of the 23 patients with tumor negative for *AR*amp, 13 had a better PSA decline on the initial NHT and ten on subsequent taxane (Fig. 5F–H). Of the ten patients with *AR*amp, one had a better percentage of PSA decline from baseline on the initial NHT and nine on subsequent taxane (RR: 5.65, bootstrapped 95% CI: 1.57–Inf, Fisher's exact $p = 0.021$).

Numerical values for the graphical representations in Fig. 5 can be found in Supplementary Tables 11 and 12.

4. Discussion

Biomarkers that identify patients who will receive differential benefit of standard of care drugs are valuable for clinical decision-making. In this study, *AR*amp was associated with decreased response, efficacy, and survival on NHT, but not on taxane chemotherapy, and this effect was significant for predictive treatment interactions with PSA response, TTNT, and OS. Patients who tested *AR*amp(+) versus *AR*amp(−) proximal to the start of NHT were far more likely to have a superior PSA response and TTNT on subsequent taxane, despite the disadvantage of having already received an additional treatment line. Therefore, *AR*amp, which was observed in 30.1% of the patients, predicted in our analysis for worse outcomes on NHT without affecting clinical benefit from taxane therapy.

Two prior observational studies reported significant associations with reduced time on treatment, but not OS, for tissue-assessed *AR* pathway alterations [27], and separately, no observed outcome associations with AR gain of function [28]. However, the authors of both studies did not distinguish between *AR* amplifications and *AR* short variant mutations, for which we did not observe the same consistency and magnitude of outcome associations as *AR*amp (Fig. 3 and 5), nor was a comparison with outcomes on taxanes reported. Single- and multisite observational studies reported predictive associations for both *AR*amp [5,6] in ctDNA and AR-V7 in CTCs [8,9], similarly observing

reduced hazards of progression and/or death on taxanes versus NHT for those testing positive for either marker. Although in practice a liquid biopsy may be more feasible for many patients, it can be confounded by low ctDNA fractions or low CTC counts [13,15], and these studies did not adjust for the factors mentioned. The reported prevalences of AR-V7 in CTCs proximal to first, second, and third+ lines are 3%, 18%, and 30%, respectively [24], while the prevalence of *AR*amp observed here is much higher (17%, 35%, and 42%, respectively; Supplementary Table 8). Notably, a recent meta-analysis of almost 1500 mCRPC patients reported the median pretherapy prevalence of *AR*amp detected in plasma across multiple prospective and retrospective studies to be 21% and 37% for first and second+ lines, respectively [14], with patients testing *AR*amp(+) prior to therapy having similarly negative NHT versus taxane outcome associations observed in our tissue-based assessments. Our observation of *AR*amp predictive associations in tumor tissue adds validity to this biomarker.

It is worth noting that the observed prevalence of *AR* short variant aberrations is much higher in liquid biopsy studies [29], which may be the result of plasma representing heterogeneous tumor deposits missed with a single tissue biopsy. While the associations of *AR* short variants with outcomes were not as strong as *AR*amp in our study, future studies reporting outcomes tied to liquid biopsy detection of *AR* short variants will refine the potential clinical implications of these aberrations.

*RB1*alt showed similar predictive associations to *AR*amp, albeit with a much lower prevalence at 5.0% in our cohort. In fact, *AR*amp and *RB1*alt demonstrated independent significant predictive associations, suggesting value for complementary assessment (Fig. 4). Prior work has reported *RB1*alt as a poor prognostic factor [30,31] and a critical component of a molecular AVPC signature [32,33], but to our knowledge, this is the first study to assess differences by NHT versus taxane drug class. Consistently, *RB1*alt is at the center of evolving biological understanding of lineage plasticity phenomena and androgen indifference in mCRPC [34].

*TP53*alt and *PTEN*alt, which are also increasingly observed in AVPC, were associated in our study with a worse PSA response on NHT but not on taxanes (Fig. 3), but with weaker associations with worse TTNT or OS. Still, *PTEN*alt was associated with PSA response, TTNT, and OS treatment interactions favoring taxane over NHT in the main cohort (Fig. 3 and 4), but in contrast to *AR*amp, this was not observed in the sequential cohort (Fig. 5) despite a similar biomarker prevalence in the two cohorts (35% vs 30%). The evidence we found is therefore not as consistent for predictive associations between NHT and taxanes for *TP53*alt or *PTEN*alt.

While we found it in only 6.1% of our cohort, *CDK12*sv(+) patients were associated with reduced OS on either drug class (Fig. 3), consistent with the findings of previous studies [35–37] and adding validity to *CDK12*sv as a poor prognostic marker in mCRPC. *SPOP*sv has previously been associated with abiraterone sensitivity and docetaxel resistance [38,39], and while worse TTNT on taxanes was observed, other observations consistent with these prior studies were not seen.

In terms of both the number of patients and biomarkers assessed, this is the largest single study to date to compare predictive biomarker assessments of NHT versus taxane chemotherapy. We used tissue samples, which are not subject to potential confounding of ctDNA fraction or CTC counts. We made use of multiple outcome measures (PSA response, TTNT, and OS) considering consistency between them when interpreting results. Our study represents diverse treatment sites and practices in the USA, with 92% of the cohort treated in nonacademic, community settings (Table 1). Using median PSA as a proxy for disease burden, our main analysis cohort (44.6 ng/ml) was comparable with the pretaxane NHT PREVAIL and COU-AA-302 studies, and with the CARD study (54.1, 42, and 60.5 ng/ml, respectively; Supplementary Table 13) [2,40,41].

Real-world data analyses hold great promise to accelerate biomarker development. Taking inspiration from randomized controlled trials, which adjust for both known and unknown imbalances, we adjusted for imbalances in two complementary ways: propensity weighting via IPTW (Fig. 3 and 4) to adjust for known imbalances in treatment assignment, and intrapatient crossover assessments of sequential drug use (Fig. 5) with individual patients being their own controls, adjusting for unknown or unquantifiable imbalances but acknowledging a disadvantage for the second treatment. To our knowledge, this is the first routine clinical practice oncology biomarker analysis that has used both these techniques in concert.

5. Limitations

This is not a randomized controlled study. Treatment assignments were at the discretion of the clinician, and while biases were considered carefully and known imbalances were adjusted, propensity adjustments are limited by the precision of measurement of clinical variables and do not adjust for unknown or unquantifiable imbalances. Simple imputation of missing clinical data may artificially decrease the variance component of the models. Patients in sequential analyses were those who were well enough to receive taxane subsequent to NHT and represent a subset of all patients. Many statistical comparisons pass nominal significance thresholds, but given the number of comparisons, results need to be interpreted with additional care. Patients who had an unsuccessful biopsy or inaccessible lesions were not represented in this study. We did not restrict by the site of biopsy or degree of anticipated ADT exposure prior to sample acquisition, reflecting pragmatic contemporary clinical specimen acquisition as much as possible. The stringent time frame imposed for sample collection limited the number of cases eligible for this analysis (Fig. 1).

Despite strong predictive associations observed in our study (and elsewhere in plasma assessments), because no interventions were directed by the findings in this study, it is not possible to definitively know whether patients who are being considered for NHT and have resistance markers detected would obtain better results if taxane use was escalated at that decision point. The most straightforward way to prospectively validate a predictive biomarker

is to screen and select patients with the alteration, and then to randomize them to receive the drug class with predictive associations linked to the biomarker versus an alternate drug class. Prospective validation of negative predictive biomarkers (ie, resistance biomarkers) in this manner would be made difficult by the necessity for some patients to be randomized to deliberately receive a drug class for which they are expected to have poor outcomes.

NHT resistance biomarkers could be used to prospectively stratify patients for clinical trials of alternative, non-NHT mechanism of action drugs, as this represents both a group for which accelerated knowledge turn is anticipated and the patient population that would be expected to obtain the most relative benefit from eventual drug approvals. Our data points to *RB1*alt, *PTEN*alt, and in particular *AR*amp as strong candidates for use to accelerate drug development.

6. Conclusions

These data support the notion that biomarkers available through routine CGP testing, specifically *AR*amp and also *RB1*alt and *PTEN*alt, are candidates for providing value for clinical decision-making by anticipating the relative efficacy and durability of standard of care NHT versus taxane treatment options.

***Author contributions*:** Ryon P. Graf had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Study concept and design: Graf.
Acquisition of data: None.
Analysis and interpretation of data: Graf, Fisher, Mateo, Zurita.
Drafting of the manuscript: Graf, Zurita.
Critical revision of the manuscript for important intellectual content: All authors.
Statistical analysis: Graf, Fisher.
Obtaining funding: Venstrom.
Administrative, technical, or material support: Venstrom.
Supervision: Zurita, Venstrom.
Other: None.

***Financial disclosures*:** Ryon P. Graf certifies that all conflicts of interest, including specific financial interests and relationships and affiliations relevant to the subject matter or materials discussed in the manuscript (eg, employment/affiliation, grants or funding, consultancies, honoraria, stock ownership or options, expert testimony, royalties, or patents filed, received, or pending), are the following: Ryon P. Graf, Virginia Fisher, Ole V. Gjoerup, Russell W. Madison, Kira Raskina, Hanna Tukachinsky, James Creeden, Rachel Cunningham, Richard S.P. Huang, Douglas A. Mata, Jeffrey S. Ross, Geoffrey R. Oxnard, and Jeffrey M. Venstrom are employees of Foundation Medicine, a wholly owned subsidiary of Roche, and have equity interest in Roche. Joaquin Mateo has served on scientific advisory boards from Amgen, AstraZeneca, Clovis Oncology, Janssen, Merck/MSD, and Roche; has participated in speaker bureaus from AstraZeneca, Guardant Health, MSD, Pfizer, Janssen, and Astellas; and has received research funding from AstraZeneca and Pfizer Oncology through grants to the institution. Amado J. Zurita reports consulting or advisory roles for AstraZeneca and Bayer, research funding to his institution from Infinity Pharma, and honoraria from Pfizer and Janssen.

***Funding/Support and role of the sponsor*:** Foundation Medicine, a wholly owned subsidiary of Roche, is a for-profit company and producer of FDA-regulated molecular diagnostics. Authors employed by Foundation Medicine were involved in the design and conduct of the study, analysis, interpretation of the data, preparation, review, and approval of the manuscript.

***Data sharing*:** Data are available for bona fide researchers who request it from the authors.

***Acknowledgments*:** We thank the patients whose data made this research possible, the clinical and laboratory staff at Foundation Medicine, and the team at Flatiron Health.

Appendix A. Supplementary material

Supplementary data to this article can be found online at https://doi.org/10.1016/j.eururo.2021.09.030.

References

[1] George DJ, Sartor O, Miller K, et al. Treatment patterns and outcomes in patients with metastatic castration-resistant prostate cancer in a real-world clinical practice setting in the United States. Clin Genitourin Cancer 2020;18:284–94.
[2] de Wit R, de Bono J, Sternberg CN, et al. Cabazitaxel versus abiraterone or enzalutamide in metastatic prostate cancer. N Engl J Med 2019;381:2506–18.
[3] Kouspou MM, Fong JE, Brew N, et al. The Movember Prostate Cancer Landscape Analysis: an assessment of unmet research needs. Nat Rev Urol 2020;17:499–512.
[4] Ballman KV. Biomarker: predictive or prognostic? J Clin Oncol 2015;33:3968–71.
[5] Conteduca V, Jayaram A, Romero-Laorden N, et al. Plasma androgen receptor and docetaxel for metastatic castration-resistant prostate cancer. Eur Urol 2019;75:368–73.
[6] Conteduca V, Castro E, Wetterskog D, et al. Plasma AR status and cabazitaxel in heavily treated metastatic castration-resistant prostate cancer. Eur J Cancer 2019;116:158–68.
[7] Annala M, Fu S, Bacon JVW, et al. Cabazitaxel versus abiraterone or enzalutamide in poor prognosis metastatic castration-resistant prostate cancer: a multicentre, randomised, open-label, phase 2 trial. Ann Oncol 2021;32:896–905.
[8] Scher HI, Lu D, Schreiber NA, et al. Association of AR-V7 on circulating tumor cells as a treatment-specific biomarker with outcomes and survival in castration-resistant prostate cancer. JAMA Oncol 2016;2:1441–9.
[9] Scher HI, Graf RP, Schreiber NA, et al. Assessment of the validity of nuclear-localized androgen receptor splice variant 7 in circulating tumor cells as a predictive biomarker for castration-resistant prostate cancer. JAMA Oncol 2018;4:1179–86.
[10] Graf RP, Hullings M, Barnett ES, Carbone E, Dittamore R, Scher HI. Clinical utility of the nuclear-localized AR-V7 biomarker in circulating tumor cells in improving physician treatment choice in castration-resistant prostate cancer. Eur Urol 2020;77:170–7.
[11] Antonarakis ES, Lu C, Luber B, et al. Clinical significance of androgen receptor splice variant-7 mRNA detection in circulating tumor cells of men with metastatic castration-resistant prostate cancer treated with first- and second-line abiraterone and enzalutamide. J Clin Oncol 2017;35:2149–56.
[12] Smerage JB, Barlow WE, Hortobagyi GN, et al. Circulating tumor cells and response to chemotherapy in metastatic breast cancer: SWOG S0500. J Clin Oncol 2014;32:3483–9.

[13] Annala M, Vandekerkhove G, Khalaf D, et al. Circulating tumor DNA genomics correlate with resistance to abiraterone and enzalutamide in prostate cancer. Cancer Discov 2018;8:444–57.
[14] Tolmeijer SH, Boerrigter E, Schalken JA, et al. A systematic review and meta-analysis on the predictive value of cell-free DNA–based androgen receptor copy number gain in patients with castration-resistant prostate cancer. JCO Precis Oncol 2020;4:714–29.
[15] Sharp A, Welti JC, Lambros MBK, et al. Clinical utility of circulating tumour cell androgen receptor splice variant-7 status in metastatic castration-resistant prostate cancer. Eur Urol 2019;76:676–85.
[16] Austin PC, Stuart EA. Moving towards best practice when using inverse probability of treatment weighting (IPTW) using the propensity score to estimate causal treatment effects in observational studies. Stat Med 2015;34:3661–79.
[17] Armstrong AJ, Luo J, Nanus DM, et al. Prospective multicenter study of circulating tumor cell AR-V7 and taxane versus hormonal treatment outcomes in metastatic castration-resistant prostate cancer. JCO Precis Oncol 2020;4, PO.20.0020.
[18] Singal G, Miller PG, Agarwala V, et al. Association of patient characteristics and tumor genomics with clinical outcomes among patients with non-small cell lung cancer using a clinicogenomic database. JAMA 2019;321:1391–9.
[19] Armstrong AJ, Lin P, Tombal B, et al. Five-year survival prediction and safety outcomes with enzalutamide in men with chemotherapy-naive metastatic castration-resistant prostate cancer from the PREVAIL trial. Eur Urol 2020;78:347–57.
[20] Frampton GM, Fichtenholtz A, Otto GA, et al. Development and validation of a clinical cancer genomic profiling test based on massively parallel DNA sequencing. Nat Biotechnol 2013;31:1023–31.
[21] Chalmers ZR, Connelly CF, Fabrizio D, et al. Analysis of 100,000 human cancer genomes reveals the landscape of tumor mutational burden. Genome Med 2017;9:34.
[22] Wasserstein RL, Lazar NA. The ASA statement on p-values: context, process, and purpose. Am Stat 2016;70:129–33.
[23] Breiman L. Random forests. Mach Learn 2001;45:5–32.
[24] Chung JH, Dewal N, Sokol E, et al. Prospective comprehensive genomic profiling of primary and metastatic prostate tumors. JCO Precis Oncol 2019;3, PO.18.00283.
[25] Lallous N, Volik SV, Awrey S, et al. Functional analysis of androgen receptor mutations that confer anti-androgen resistance identified in circulating cell-free DNA from prostate cancer patients. Genome Biol 2016;17:10.
[26] Torquato S, Pallavajjala A, Goldstein A, et al. Genetic alterations detected in cell-free DNA are associated with enzalutamide and abiraterone resistance in castration-resistant prostate cancer. JCO Precis Oncol 2019;3, PO.18.00227.
[27] Abida W, Cyrta J, Heller G, et al. Genomic correlates of clinical outcome in advanced prostate cancer. Proc Natl Acad Sci U S A 2019;116:11428–36.
[28] Chen WS, Aggarwal R, Zhang L, et al. Genomic drivers of poor prognosis and enzalutamide resistance in metastatic castration-resistant prostate cancer. Eur Urol 2019;76:562–71.
[29] Tukachinsky H, Madison RW, Chung JH, et al. Genomic analysis of circulating tumor DNA in 3,334 patients with advanced prostate cancer identifies targetable BRCA alterations and AR resistance mechanisms. Clin Cancer Res 2021;27:3094–105.
[30] Hamid AA, Gray KP, Shaw G, et al. Compound genomic alterations of TP53, PTEN, and RB1 tumor suppressors in localized and metastatic prostate cancer. Eur Urol 2019;76:89–97.
[31] Chen WS, Alshalalfa M, Zhao SG, et al. Novel RB1-loss transcriptomic signature is associated with poor clinical outcomes across cancer types. Clin Cancer Res 2019;25:4290–9.
[32] Aparicio AM, Shen L, Tapia EL, et al. Combined tumor suppressor defects characterize clinically defined aggressive variant prostate cancers. Clin Cancer Res 2016;22:1520–30.
[33] Corn PG, Heath EI, Zurita A, et al. Cabazitaxel plus carboplatin for the treatment of men with metastatic castration-resistant prostate cancers: a randomised, open-label, phase 1–2 trial. Lancet Oncol 2019;20:1432–43.
[34] Yamada Y, Beltran H. Clinical and biological features of neuroendocrine prostate cancer. Curr Oncol Rep 2021;23:15.
[35] Rescigno P, Gurel B, Pereira R, et al. Characterizing CDK12-mutated prostate cancers. Clin Cancer Res 2021;27:566–74.
[36] Reimers MA, Yip SM, Zhang L, et al. Clinical outcomes in cyclin-dependent kinase 12 mutant advanced prostate cancer. Eur Urol 2020;77:333–41.
[37] Antonarakis ES, Isaacsson Velho P, Fu W, et al. CDK12-altered prostate cancer: clinical features and therapeutic outcomes to standard systemic therapies, poly (ADP-ribose) polymerase inhibitors, and PD-1 inhibitors. JCO Precis Oncol 2020;4:370–81.
[38] Boysen G, Rodrigues DN, Rescigno P, et al. SPOP-mutated/CHD1-deleted lethal prostate cancer and abiraterone sensitivity. Clin Cancer Res 2018;24:5585–93.
[39] Shi Q, Zhu Y, Ma J, et al. Prostate Cancer-associated SPOP mutations enhance cancer cell survival and docetaxel resistance by upregulating Caprin1-dependent stress granule assembly. Mol Cancer 2019;18:170.
[40] Beer TM, Armstrong AJ, Rathkopf DE, et al. Enzalutamide in metastatic prostate cancer before chemotherapy. N Engl J Med 2014;371:424–33.
[41] Ryan CJ, Smith MR, de Bono JS, et al. Abiraterone in metastatic prostate cancer without previous chemotherapy. N Engl J Med 2013;368:138–48.