A correlative biomarker study and integrative prognostic model in chemotherapy-naïve metastatic castration-resistant prostate cancer treated with enzalutamide

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Abstract

Background: There is a considerable need to incorporate biomarkers of resistance to new antiandrogen agents in the management of castration-resistant prostate cancer (CRPC).

Methods: We conducted a phase II trial of enzalutamide in first-line chemo-naïve asymptomatic or minimally symptomatic mCRPC and analyzed the prognostic value of TMPRSS2-ERG and other biomarkers, including circulating tumor cells (CTCs), androgen receptor splice variant (AR-V7) in CTCs and plasma Androgen Receptor copy number gain (AR-gain). These biomarkers were correlated with treatment response and survival outcomes and developed a clinical–molecular prognostic model using penalized co-proportional hazard model. This model was validated in an independent cohort.

Results: Ninety-eight patients were included. TMPRSS2-ERG fusion gene was detected in 32 patients with no differences observed in efficacy outcomes. CTC detection was associated with worse outcome and AR-V7 in CTCs was associated with increased rate of progression as best response. Plasma AR gain was strongly associated with an adverse outcome, with worse median prostate specific antigen (PSA)-PFS (4.2 vs. 14.7 m; \( p < 0.0001 \)), rad-PFS (4.5 vs. 27.6 m; \( p < 0.0001 \)), and OS (12.7 vs. 38.1 m; \( p < 0.0001 \)). The clinical prognostic model developed in PREVAIL was validated (C-Index 0.70) and the addition of plasma AR (C-Index 0.79; \( p < 0.001 \)) increased its prognostic ability. We generated a parsimonious model including alkaline phosphatase (ALP); PSA and AR gain (C-index 0.78) that was validated in an independent cohort.

Conclusions: TMPRSS2-ERG detection did not correlate with differential activity of enzalutamide in first-line mCRPC. However, we observed that CTCs and plasma AR gain were the most relevant biomarkers.

KEYWORDS
AR gain, AR-V7, CTCs, enzalutamide, prostate cancer, TMPRSS2-ERG

1 | INTRODUCTION

Prostate cancer (PCa) is the second cause of death from cancer in males.\(^1\) Its growth is dependent upon androgen receptor (AR) signaling, and androgen deprivation therapy (ADT) is the mainstay of treatment in advanced patients.\(^2\) Virtually all patients progress to a castration-resistant state where androgen signaling is potentially driving tumor progression.\(^3\) Enzalutamide is a potent AR-targeted agent that competitively binds the AR ligand-binding domain and inhibits AR signaling.\(^4\) Treatment with enzalutamide has
improved overall survival and quality of life in PCa. However benefit from this treatment is variable and several clinical and molecular events have been proposed to explain this heterogeneity.

Fusion genes involving E26 transformation-specific (ETS) oncogenes are the most common driver events affecting 30%–70% of PCa. The most frequent fusion gene involves transmembrane protease serine 2 (TMPRSS2) on 21q22.3 and v-ets erythroblastosis virus E26 oncogene homolog (ERG) on 21q22.2, either by intrachromosomal deletion or translocation, and as a result of the oncoprotein ERG becomes AR-regulated. TMPRSS2-ERG is involved in tumor initiation, invasion, and progression, and has been associated with increased efficacy in abiraterone-treated patients. Other biomarkers, including plasma AR gain, circulating tumor cells (CTCs), and AR-V7 in CTCs have demonstrated prognostic and/or predictive value in pretreated metastatic castration-resistant prostate cancer (mCPRC). However, the prognostic value of these biomarkers in first-line mCPRC needs to be further explored.

Clinical prognostic models in mCPRC, including a prognostic model in patients treated with enzalutamide in first-line mCPRC are intended to deal with this heterogeneity. This latter model needs to be externally validated and can potentially be improved including molecular information.

In this phase 2 multicenter biomarker study with enzalutamide in first-line chemo-naïve mCPRC, we aimed to evaluate the clinical significance of TMPRSS2-ERG fusion gene, and to explore other relevant biomarkers, including plasma AR, CTCs, and AR-V7 in CTCs, and its contribution to the available clinical prognostic models.

## 2 MATERIALS AND METHODS

### 2.1 Study design and conduct

The PREMIERE trial is a translational multicenter single-arm open-label phase 2 clinical trial (NCT02288936) of enzalutamide in first-line mCPRC, originally designed to analyze the prognostic value of the gene fusion TMPRSS2-ERG and other correlative laboratory studies, including plasma DNA and CTC analysis. The study was approved by a central independent review board (IRB).

The validation cohort consisted of a single institution cohort from patients participating in a protocol approved by the Istituto Scientifico Romagnolo per lo Studio e la Cura dei Tumori (IRST), Meldola, Italy (REC 2192/2013) with plasma samples collected prospectively with the primary aim of biomarker evaluation.

### 2.2 Participants

The PREMIERE trial consisted of patients with histologically confirmed adenocarcinoma of the prostate with documented metastases and tumor progression and a serum testosterone level of 50 ng per deciliter or less with continued androgen-deprivation therapy. Eligible patients had Eastern Cooperative Oncology Group (ECOG) 0–1, and were asymptomatic or mildly symptomatic (Brief Pain Inventory Short Form question 3 of less than 4).

The IRST cohort consisted of patients with histologically confirmed prostate adenocarcinoma without neuroendocrine differentiation, progressive disease despite “castration levels” of serum testosterone (<50 ng/dl), ongoing LHRH analog treatment or prior surgical castration, and no prior treatment with enzalutamide or abiraterone.

Treatment in both cohorts consisted of enzalutamide at a dose of 160 mg once daily. Treatment continued until the occurrence of unacceptable side effects or confirmed radiographic progression. Written informed consent was obtained from all patients.

### 2.3 Procedures

In the PREMIERE trial, tumor tissue and blood samples were shipped before study entry and a central pathologist reviewed all histological FFPE samples. Blood samples were collected before study entry, at 12 weeks and at progression, and included three 5 ml EDTA tubes: one were locally processed to obtain plasma that was stored at −80°C and centrally shipped at study completion and one was shipped overnight at 4°C to a central laboratory and processed in less than 24 h for CTC analyses. In the IRST cohort, plasma samples were collected before treatment initiation and analyzed at a central laboratory.

**TMPRSS2-ERG fusion gene** was studied in FFPE tumor tissue from the PREMIERE trial. In brief, an 8-μm FFPE slide was macrodissected and DNA/RNA was extracted and quantitative PCR (qPCR) was performed in duplicate with the TaqMan primer probe for TMPRSS2-ERG fusion transcript (Hs03063375 ft, Applied Biosystems) following manufacturer’s instructions. ERG immunohistochemistry was performed using ERG rabbit monoclonal antibody (EPR3864, Epitomics; dilution 1:100) and correlated with qPCR results. Fluorescence in situ hybridization (FISH) for TMPRSS2-ERG fusion gene was independently performed as previously described at two different institutions (HMM and CNIO).

- **Plasma AR copy number.** Plasma was collected within 30 days before treatment initiation and plasma aliquots were stored at −80°C and centrally analyzed upon study completion. ddPCR assays were carried out as previously described. In brief, for each sample, AR CN was estimated using each of the reference genes NSUN3, EIF2C1, and AP3B1 and using ZXDB at Xp11.21 as a control gene to determine X chromosome CN. An AR gain cutoff of ≥1.92 was considered as AR gain, as previously published.

- **CTC and AR-V7 analysis.** The CTC analyses were conducted using the commercially available AdnaTest platform (Qiagen) following the manufacturer’s instructions with a minor modification previously described. Custom primers, as previously described, were used to detect AR-V7 mRNA. Sanger sequencing confirmed the accuracy of the PCR product. AR-V7 cross-validation was
2.4 | Outcomes

The primary endpoint for the PREMIERE clinical trial was prostate specific antigen (PSA) progression-free survival (PSA-PFS) and secondary endpoints included PSA response, radiographic progression-free survival (rad-PFS), and overall survival (OS). PSA and blood tests were assessed monthly and radiographic disease was evaluated with the use of computed tomography (CT) and bone scan at the time of screening and every 12 weeks thereafter. Response was evaluated according to the Prostate Cancer Clinical Trials Working Group 2 (PCWG2) criteria and soft tissue disease was assessed on the basis of Response Evaluation Criteria in Solid Tumors (RECIST), version 1.1. CTC conversion was defined considering the analysis at basal and after 12 weeks of treatment.

2.5 | Statistical analyses

Statistical analyses were performed using the R software, version 3.3.0. The statistical plan for biomarkers included descriptive and prognostic analyses of TMPRSS2-ERG, CTC, AR-V7 in CTCs, and AR gain using the primary and secondary outcomes of the trial, as previously described. Post hoc exploratory analyses included correlation with primary progression. Qualitative variables were compared using the Fisher exact test. Time variables were evaluated using Kaplan-Meier analysis and cox-proportional hazards models. All tests were two-sided, and an alpha-error of less than 0.05 was required to be considered statistically significant. Cohen’s Kappa test was used to study concordance between the central and the external laboratory. A Cox-proportional hazards model via penalized maximum likelihood, using the package glmnet 2.0, was used to generate a parsimonious clinical-molecular model.

3 | RESULTS

Ninety-eight chemotherapy-naïve mCRPC patients initiated enzalutamide as first-line treatment between February and November 2015 at 16 Spanish institutions in the PREMIERE trial. Patients’ characteristics are described in Table 1. Survival outcomes for all patients included in the study are shown in Supporting Information: Figure S1. With a median follow-up of 37 months, median PSA-PFS was 14.1 months (95% confidence interval [CI]: 10.2–20.2), median rad-PFS was 25.2 months (95% CI: 21.7–32.1) and median OS was 37.5 months (95% CI: 33.7 vs. NR). Treatment responses are described in Supporting Information: Table S2. PSA-50 (decrease ≥50%) was observed in 82%, and PSA-90 (decrease ≥90%) in 53%, with radiographic response observed in 49% of the patients (N = 21).

Enzalutamide was well tolerated with no unexpected toxicities, as shown in Supporting Information: Table S4.

3.1 | TMPRSS2-ERG status

TMPRSS2-ERG fusion gene was detected in 32 patients (33%). All positive samples expressed high ERG in the nucleus by IHC (r = 0.93; p < 0.0001). Baseline patients’ characteristics were similar between both groups and no differences were observed in any efficacy outcome based on the detection of TMPRSS2-ERG. Further details are described in Supporting Information: Tables S1–S3 and Figures S2 and S3.
3.2 | Plasma AR gain

Baseline plasma AR gain was detected in 11 patients (11%). Plasma AR-based survival analyses are shown in Figure 1A–C. AR gain was associated with worse survival outcomes than AR normal: median PSA-PFS 4.2 versus 14.7 months (hazard ratio [HR] 4.03, 95% confidence interval [CI] 1.87–8.72; p < 0.001), median rad-PFS was 4.5 versus 27.6 months (HR 9.83, 95% CI 4.50–21.44; p < 0.001) and median OS of 12.7 versus 38.1 months (HR 6.65, 95% CI 3.18–13.91; p < 0.0001), respectively. AR gain was also associated with worse PSA response, as shown in Figure 1D.

AR gain was detected in 19.4% (6/31) versus 7.6% (5/66) in TMPRSS2-ERG positive and negative, respectively (p = 0.166), as shown in Supporting Information: Table S5.

3.3 | CTCs by Adna-Test®

Baseline CTCs were present in 35 patients (36%). Survival outcomes by baseline CTC status are described in Figure 2A–C. The presence of CTC at baseline was associated with worse evolution in all survival outcomes. Median PSA-PFS for positive patients was 7.4 versus 20.2 months (HR 3.37, 95% CI 2.01–5.66; p < 0.0001), median rad-PFS was 11.5 versus 33.1 months (HR 5.21, 95% CI 2.82–9.64; p < 0.0001) and median OS was 25.4 months versus not reached (HR 4.68, 95% CI 2.64–8.28; p < 0.0001). CTC conversion analysis using landmark survival analysis is shown in Figure 2D. Conversion of CTC detection from positive to negative was associated with improved evolution in all survival outcomes, including PSA-PFS (p < 0.001), rad-PFS (p < 0.001), and OS (p < 0.001). No association was observed between TMPRSS2-ERG expression and CTC detection (p = 0.825), as described in Supporting Information: Table S5.

3.4 | AR-V7 expression in CTCs

AR-V7 was detected in 16% of CTC-positive evaluable patients (5/32). Progression as best response at 12 weeks was observed in 60% (3/5) in AR-V7 positive patients, compared with 30% (8/27) in AR-V7 negative and 8% (5/63) in CTC negative patients (p = 0.0014). However, two externally validated AR-V7 patients had tumor responses lasting for 14 and 25 months, as shown in Supporting Information: Figure S4A. AR-V7-based survival analyses are shown in Figure 2B–D. No differences were observed for survival outcomes. Intriguingly, at baseline all AR-V7 positive patients were TMPRSS2-ERG negative (5/21 vs. 0/11, p = 0.134), as shown in Supporting Information: Table S5. A numerical increase, not statistically significant, was observed for AR gain in AR-V7 positive when compared with AR-V7 negative and CTC negative patients: 40% (2/5), 16% (4/24), and 8% (5/66), respectively.
3.5 | Development of an integrated clinical–molecular model

We evaluated in our series the clinical prognostic model previously developed based on the PREVAIL trial externally validating it in our series, with a Concordance Index (C-Index) of 0.70. Interestingly, most patients in our study were included in the low (61%) and intermediate (37%) risk groups, as shown in Supporting Information: Figure S5.

A multivariate analysis of all clinical variables included in the clinical model, CTC, and AR is shown in Table 2. We then integrated AR gain with the clinical variables included in the clinical model into a new comprehensive clinical and molecular model that obtained a bootstrap-validated C-Index of 0.79. The addition of AR to the clinical model increased the prognostic ability of the clinical model (p < 0.001). Using a penalized regression model, we obtained a clinical–molecular parsimonious model that included three variables: ALP ratio, PSA, and AR gain Table 3, and a bootstrap-validated C-Index of 0.78. This model was validated in an independent cohort of patients treated at IRST with enzalutamide obtaining a C-Index of 0.71. We then designed a nomogram capable to predict the survival probability at 12, 24, and 36 months, as shown in Figure 3.

4 | DISCUSSION

We here show the final results of a biomarker phase 2 multicentre clinical trial of enzalutamide in first-line chemo-naïve mCRPC. The primary aim of the study was to evaluate the association between TMPRSS2-ERG and the efficacy of enzalutamide and we did not find any difference. However, we observed that CTCs by AdnaTest® and AR gain are strong and independent prognostic variables. In addition, we externally validated a clinical prognostic model developed in the PREVAIL trial and observed that both CTCs and AR gain are able to improve the prognostic ability of the model. We then developed a parsimonious model including clinical variables and AR gain, that validated an independent data set of mCRPC patients treated with enzalutamide in the same clinical scenario.
Previous results regarding the predictive value of TMPRSS2-ERG to new antiandrogens were controversial with abiraterone, with an early phase I/II trial of abiraterone that reported increased PSA responses in TMPRSS2-ERG associated tumors.15,29 Our results with enzalutamide-treated patients, together with previous studies with abiraterone, support that TMPRSS2-ERG fusion gene has limited value as predictive biomarker in mCRPC treated with anti-androgen therapies.

We also evaluated plasma AR-gain and other promising biomarkers including CTCs measured by AdnaTest® and AR-V7 expression in CTCs. We previously published the association of plasma AR-gain with an adverse outcome to enzalutamide with a median follow-up of 11 months. Here we present the final updated survival, with a median follow-up of 37 months that confirms its strong independent prognostic value in first-line mCRPC. AR-gain prognostic value was independent of other clinical and molecular prognostic variables. We observed a numerical increase in AR gain in AR-V7 positive patients compared with AR-V7 negative and CTC negative (40% vs. 17% vs. 8%). This result, although limited by the low numbers, is in agreement with previous publications in PCa metastatic tissue, that observe an association between AR gain and AR-V7 expression in PCa metastases.30

We show that CTCs can be detected using AdnaTest® in almost one third (35%) of low-intermediate risk mCRPC patients, and that it is a strong and independent prognostic biomarker. We also observe, using landmark survival analysis, that CTC conversion at 12 weeks of treatment is associated with treatment outcome, including a favorable outcome when it turns negative and an adverse outcome when it becomes positive. However, prospective randomized clinical trials are needed to fulfill the Prentice criteria31 and fully qualify as a meaningful biomarker for regulatory matters.

AR-V7 in CTCs has previously demonstrated clinical value in mCRPC patients treated with a new anti-androgen therapy.22,23 In this first-line study, we observed a low detection rate for AR-V7 (5% of all

<table>
<thead>
<tr>
<th>TABLE 2</th>
<th>Multivariable analysis for the clinical and molecular variables</th>
</tr>
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<tbody>
<tr>
<td><strong>Premiere</strong></td>
<td><strong>Prognostic</strong></td>
</tr>
<tr>
<td>Albumin</td>
<td>0.57 (0.21–1.57)</td>
</tr>
<tr>
<td>ALP</td>
<td>0.44 (0.23–0.87)</td>
</tr>
<tr>
<td>Number of bone metastases</td>
<td>0.94 (0.82–1.08)</td>
</tr>
<tr>
<td>Hemoglobin</td>
<td>1.00 (0.79–1.27)</td>
</tr>
<tr>
<td>LDH</td>
<td>0.66 (0.35–1.26)</td>
</tr>
<tr>
<td>NLR</td>
<td>0.77 (0.36–1.64)</td>
</tr>
<tr>
<td>Pain score</td>
<td>2.13 (1.12–4.05)</td>
</tr>
<tr>
<td>Pattern of spread</td>
<td>0.63 (0.14–2.83)</td>
</tr>
<tr>
<td>Loge PSA</td>
<td>1.39 (1.10–1.74)</td>
</tr>
<tr>
<td>Time from diagnosis to randomization</td>
<td>1.00 (0.99–1.01)</td>
</tr>
<tr>
<td>AR gain</td>
<td>8.25 (3.17–21.45)</td>
</tr>
<tr>
<td>CTC</td>
<td>2.74 (1.34–5.61)</td>
</tr>
</tbody>
</table>

Abbreviations: ALP, alkaline phosphatase; AR, androgen receptor; BPI, Brief Pain Inventory; CI, confidence interval; CTC, circulating tumor cell; ECOG, Eastern Cooperative Oncology Group; HR, hazard ratio; LDH, lactate dehydrogenase; NLR, neutrophil to lymphocyte ratio.

*p Value was calculated using Cox regression.

<table>
<thead>
<tr>
<th>TABLE 3</th>
<th>Clinical–molecular parsimonious model</th>
</tr>
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<tr>
<td><strong>Coefficient</strong></td>
<td><strong>p</strong></td>
</tr>
<tr>
<td>ALP ratio (log)</td>
<td>0.73</td>
</tr>
<tr>
<td>PSA ng/dl (log)</td>
<td>0.36</td>
</tr>
<tr>
<td>AR gain (yes vs. no)</td>
<td>2.15</td>
</tr>
</tbody>
</table>

*p Value was calculated using Cox regression.

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**FIGURE 3** Nomogram for the clinical–molecular parsimonious model. Nomogram developed using the integrated parsimonious three variables prognostic model. ALP ratio and PSA were included in logarithmic scale. This nomogram predicts survival probability at 12, 24, and 36 months. ALP, alkaline phosphatase.
patients; N = 5/98) and low PSA50 response rate (40% vs. 82%). These results are consistent with a recently published phase 3 trial in this same scenario, with a detection rate of 7%–10% (N = 38/953) and a response rate of 42% in 19 patients treated with enzalutamide.

Investigators from the pivotal trial of enzalutamide in first-line mCRPC published a clinical prognostic model able to stratify patients based on pretreatment clinical variables. This model was limited by the lack of external validation and the absence of molecular variables. We here validated this clinical prognostic model, obtaining a C-index of 0.70 and observed that both CTCs and AR-gain were independent variables that were able to improve the prognostic ability of the model. We then built a parsimonious clinical–molecular model, composed of three variables: AR gain, ALP, and PSA that was independently validated. LDH has been previously selected in multiple prognostic models in mCRPC, including models that include CTCs. Intriguingly, LDH was not significant in our penalized regression model. The association of LDH with high-risk features, that were not represented in our model, might explain the lack of statistical significance in our study.

5 | CONCLUSIONS

In this phase 2 biomarker trial, we report additional evidence with long follow-up on the prognostic impact of AR gain together with other biomarkers, including CTCs and AR-V7 chemo-naïve mCRPC patients. We demonstrate its ability to improve clinical prognostic models and propose a new parsimonious model including plasma AR gain. Further studies, including comprehensive biomarker panels and well-annotated clinical data sets, are required to redefine prognostic models in PCa.

ACKNOWLEDGMENTS

The authors would like to acknowledge all the staff at SOGUG for their support to run the PREMIERE trial, Astellas for supporting this research, ISCIII from the Spanish Ministry of Health, and Cris Cancer Foundation for their support. This trial was promoted by SOGUG and received a grant from Astellas. EGB received a travel grant (BA16/00038) and funding support from the “Instituto de Salud Carlos III” (PI18/00883) and support from SEOM-CRIS Cancer Foundation.

CONFLICTS OF INTEREST

TG has received travel grants from Sanofi and participated in advisory boards for Sanofi, Janssen, Astellas, and Bayer. AF has received travel grants from Astellas, Astra-Zeneca, Sanofi and participated in advisory boards for Janssen, Sanofi, Eisai, and Bayer. SVE has received travel grants from Astellas, Janssen, and Bayer, and has participated in advisory boards for Janssen, Astellas, Sanofi, and Bayer. AGdA has received research funding from Astellas, travel grants from Astellas, Janssen, Sanofi, BMS, Roche, Pfizer, and Ipsen, and honoraria for speaker engagements, advisory boards, and continuous medical education from Janssen, Astellas, Sanofi, Bayer, Roche, Ipsen, BMS, MSD, Pfizer, Eusa Pharma, Eisai, and Astra Zeneca. ESA is the codeveloper of a patented AR-V7 biomarker technology that has been licensed to Qiagen. ID has received travel grants and research funding from Astellas and has participated in advisory boards for Astellas, Janssen, Sanofi, and Bayer. EG has received travel grants from Astellas, Janssen, Sanofi, Bayer, Roche, BMS, and Eisai, honoraria for speaking engagements for Astellas, Janssen, Sanofi, Bayer, Pfizer, Roche, BMS, Novartis, Rovi, Daiichi Sankyo, Leo Pharma, Menarini, Eisai, MSD, Boehringer Ingelheim, Merck, and EUSA Pharma and participated in advisory boards for Astellas, Janssen, Sanofi, Bayer, Pfizer, Roche, Novartis, Eisai, EUSA Pharma, BMS, AstraZeneca, Merck, Rovi, Daiichi Sankyo, and Techdow. JP has received research funding from Astellas and Roche and received honoraria for speaker engagements, advisory roles, or continuous medical education from Astellas, Astra Zeneca, Janssen, MSD, Bayer, Pfizer, Eisai, Ipsen, Sanofi, Roche, BMS, and Merck. BM has served advisory role from Roche, Sanofi, Janssen, Astellas, Pfizer, Novartis, Bristol-Myers Squibb, and Ipsen, research funding from Roche, Bayer, and Janssen, and accommodation expenses from Pfizer and Janssen. MA Climent has received travel grants from Astellas, Janssen, Sanofi, Pfizer, Roche, and Ipsen. And honoraria for speaker engagements, advisory boards, and continuous medical education from Janssen, Astellas, Sanofi, Bayer, Roche, Ipsen, BMS, MSD, Pfizer, and Astra Zeneca MIMV has received travel grants from Astellas and Janssen and has participated in advisory boards for Janssen, Astellas, Sanofi, and Bayer. María Isabel Sáez Medina has received travel grants from Sanofi and Roche and participated in advisory boards from Sanofi, Ipsen, and Astellas. DC has received research funding from Astellas, educational grants from Pfizer and Janssen, travel grants from Pfizer and BMS, and has participated in advisory boards for Pfizer, Astellas, Janssen, Sanofi, Bayer, and Roche. JL is an inventor of AR-V7-related technologies that have been licensed to A&G Pharmaceuticals and Qiagen. GA reported receiving grants, personal fees, nonfinancial support, and speaker fees from Janssen, Astellas, and Sanofi; personal fees, nonfinancial support, and speaker fees from AstraZeneca; and personal fees from Novartis and Bayer outside the submitted work; in addition, GA reported having a patent (GB1915469.9; blood signatures for prostate cancer detection) pending and is on the Institute of Cancer Research list of rewards to inventors for abiraterone acetate. EG Research funding from Astellas, Astra Zeneca, IPSEN, Pfizer, Roche and has participated in advisory boards for Adacap, AMGEN, Angelini, Astellas, Astra Zeneca, Bayer, Blueprint, Bristol Myers Squibb, Caris Life Sciences, Celgene, Clovis Oncology, Eisai, Eusa Pharma, Genetracer, Guardant Health, HRA Pharma, IPSEN, ITM-Radiopharma, Janssen, Lexicon, Lilly, Merck KGAa, MSD, Nanostring Technologies, Natera, Novartis, ONCODNA (Biosequence), Palex, Pharmamar, Pierre Fabre, Pfizer, Roche, Sanofi, Genzyme, Servier, Taiho, Thermo Fisher Scientific. EGB has received travel grants from Astellas, Janssen, and Sanofi and has participated in advisory boards for Astellas, Janssen, Sanofi, Astra-Zeneca, and Bayer.

DATA AVAILABILITY STATEMENT

The authors confirm that the data supporting the findings of this study are available within the article and its Supporting Information.

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REFERENCES

SUPPORTING INFORMATION
Additional supporting information can be found online in the Supporting Information section at the end of this article.

How to cite this article: Fernandez-Perez MP, Perez-Navarro E, Alonso-Gordoa T, et al. A correlative biomarker study and integrative prognostic model in chemotherapy-naïve metastatic castration-resistant prostate cancer treated with enzalutamide. The Prostate. 2023;83:376-384. doi:10.1002/pros.24469