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Prostate Cancer

Prognostic Score and Benefit from Abiraterone in First-line Metastatic, Castration-resistant Prostate Cancer

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Abstract

Background: Most available prognostic nomograms in metastatic castration-resistant prostate cancer (mCRPC) are derived from datasets not representative of the current treatment landscape. A prognostic nomogram for first-line mCRPC treatment was developed from patients treated in the PREVAIL study.
Objective: To validate the Armstrong model in the COU-AA-302 trial.
Design, setting, and participants: A post hoc analysis of mCRPC patients treated in the COU-AA-302 trial was carried out (NCT00887198).
Outcome measurements and statistical analysis: The Armstrong prognostic model was applied to patients treated in COU-AA-302. A continuous risk score was derived from coefficients from the original model. Time-dependent area under the curve (tAUC) was used to evaluate the overall predictive ability of the model. Patients were categorized according to the number of risk factors present into those at a low (three or fewer risk factors), intermediate (four to six risk factors), and high (seven to ten risk factors) risk. The association with survival was assessed with Cox regression models. Interaction tests were used to assess the impact of treatment arm in each of the prognostic groups.
Results and limitations: A total of 1088 patients were analyzed. The risk score was associated with overall survival (OS; tAUC 0.733). Most patients were at a low (49%) or intermediate (41%) risk. Risk category was significantly associated with OS (hazard ratio [HR]: 2.3; 95% confidence interval [CI]: 1.9–2.4; $p < 0.001$), radiographic progression-free survival (rPFS; HR: 1.7; 95% CI: 1.5–1.8; $p < 0.001$), and prostate-specific antigen progression-free survival (HR: 1.7; 95% CI: 1.5–1.9; $p < 0.001$). A significant interaction between risk group and OS ($p = 0.007$) and rPFS ($p = 0.009$) was observed. Survival was superior in low-risk patients (HR: 0.73; 95% CI: 0.59–0.89; $p = 0.009$), but similar in intermediate-risk (HR: 0.97; 95% CI: 0.79–1.21; $p = 0.9$) and high-risk (HR: 1.35; 95% CI: 0.80–2.28; $p = 0.5$) patients. Two-year OS rates in abiraterone versus placebo were 82% versus 74% in low-risk, 55% versus 52% in intermediate-risk, and 28% versus 31% in high-risk patients.

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Conclusions: We validate the prognostic value of the Armstrong risk model in patients treated with first-line androgen receptor signaling inhibitors. Abiraterone provided a greater benefit in low-risk patients with less aggressive disease. Further research is needed to establish the role of Armstrong risk groups for treatment selection in mCRPC patients.
Patient summary: In this report, we validated the Armstrong nomogram in the COU-AA-302 trial population. We found a similar prognostic performance to that of the original model. Good-risk patients received the greatest benefit from abiraterone.

1. Introduction

Prostate cancer is the most common malignancy in men. Metastatic castration-resistant prostate cancer (mCRPC) represents the final and lethal phase of the disease, and is a major cause of morbidity and mortality worldwide. In recent years, the development of novel therapeutic agents has significantly increased the life expectancy of mCRPC patients [1–6]. However, significant clinical heterogeneity exists, with some patients presenting with low-volume disease and an indolent course, and others suffering aggressive, rapidly progressing disease.

Over the past years, a number of different prognostic models based on post hoc analyses of phase 3 clinical trials have been developed [7–9]. These models incorporate a number of clinical, radiographic, and laboratory parameters, combined into nomograms, to predict the probability of survival at 1, 2, and/or 3 yr. Prognostic nomograms have shown utility for an individualized estimation of prognosis and are also useful for the stratification of patients in clinical trials [10]. Owing to the rapid shift in the therapeutic landscape of prostate cancer, with newer agents being increasingly used in earlier stages of the disease, many of these prognostic models were derived from clinical trial datasets that do not represent the current mCRPC patient population. Some models for first- and second-line mCRPC patients [7–9,11], for instance, were developed before the incorporation of androgen receptor signaling inhibitors (ARSIs) such as abiraterone and enzalutamide, making survival estimates no longer valid [12]. Recently, Armstrong and colleagues [13,14] developed a prognostic nomogram based on the data from the PREVAIL trial, comparing enzalutamide versus placebo as first-line therapy in a mildly symptomatic mCRPC patient population, and were able to prove a significant association with overall survival (OS), radiographic progression-free survival (rPFS), and prostate-specific antigen (PSA) progression-free survival (PFS). A second survival model, based on the COU-AA-302 trial, has also been developed for the assessment of rPFS [15].

In the absence of molecular biomarkers with predictive value for the majority of patients with mCRPC, clinical decision-making continues to rely heavily on the prognostic assessment of the "aggressiveness" of the disease. Prognostic tools may be useful for the identification of poor-risk patients who may require immediate treatment initiation in order to prevent short-term clinical deterioration. Despite the improvement in prognostic estimations with contemporary models, there is currently no evidence on the relationship between clinical risk models and benefit from treatment. The development of clinical or molecular biomarkers to aid the selection of first-line treatment in advanced prostate cancer remains, to date, a critical unmet need.

In this study, we aimed to externally validate the Armstrong nomogram model with data from patients treated in the COU-AA-302 trial and to evaluate the impact of abiraterone on survival in each of the risk groups.

2. Patients and methods

2.1. Patients

Patients treated in the COU-AA-302 were included in this validation study. Briefly, treatment-naïve mCRPC patients who were asymptomatic or mildly symptomatic were treated with abiraterone acetate 1000 mg daily + prednisone 5 mg twice daily (experimental arm) or placebo + prednisone 5 mg twice daily (control arm). The population of the COU-AA-302 trial is generally considered to have a similar prognosis to that of the PREVAIL trial, used for the development of the Armstrong nomogram. Characteristics of the COU-AA-302 study, including inclusion criteria and main results, have been published elsewhere [2].

2.2. Statistical analysis

The primary endpoint of the study was OS. Secondary endpoints included rPFS, PSA PFS, and confirmed PSA response rates, as defined in Supplementary Table 1 [13]. Quality of life was assessed by the FACT-P questionnaire, performed at baseline and specific time points, as has been published previously [16].

The Armstrong model was applied to patients participating in the COU-AA-302 trial. As described in Supplementary Table 2, variables included in the model were albumin, alkaline phosphatase (ALP), hemoglobin, lactate dehydrogenase (LDH), neutrophil to lymphocyte ratio (NLR), number of bone metastases (NBM), presence of pain, PSA, time from diagnosis to randomization (TDR), pattern of spread (PoS; essentially visceral vs bone vs lymph node only involvement), and treatment arm (enzalutamide vs placebo). Predictive mean matching was performed to impute missing values (Supplementary Fig. 1). We compared the distribution of variables between the COU-AA-302 and PREVAIL trials by performing one-proportion Z tests, where data reported in the PREVAIL trial were used as the expected proportion.

An individual risk score was calculated for each patient according to the following formula:

$$\begin{aligned}\text{Riskscore} = \exp(&-0.344\times albumin+0.235\times ALP-0.166\\ &\times +0.408\times LDH+0.378\times NLR+0.381\times NBM+0.262\\ &\times pain+0.707\times PoS+0.204\times log\text{GPSA}-0.003\times\text{TDR}\\ &+0.389\times\text{treatment})\end{aligned}$$

First, we validated the Armstrong prognostic model with the risk score as a continuous variable. We assessed the predictive accuracy of the model comparing predicted and actual OS, rPFS, and PSA PFS, using time-dependent area under the curve (tAUC) methods to plot the predicted versus observed probability of events at 3-mo intervals between 6 and 39 mo. Patients were categorized into three groups based on the tertiles of the distribution of the prognostic score in our dataset, and into low (three or fewer risk factors), intermediate (four to six risk factors), and high (seven to ten risk factors) risk groups based on the number of Armstrong risk factors present (Supplementary Table 2).

The heterogeneity of treatment effect was assessed by evaluating the interaction term between the treatment arm and the risk group in Cox regression models. For this purpose, the treatment arm was removed as a cofactor in the risk group classification in order to suppress its potential confounding role. Median survival times and event-free survival rates at 12, 24, and 36 mo were compared in abiraterone versus placebo-treated patients in each of the risk groups.

Associations of time to event variables were assessed with Cox regression models. Kaplan-Meier estimates of median and 95% confidence interval (CI) were calculated. Logistic regression models were used to assess differences in PSA or radiographic response rates. All statistical tests used were two sided. All p values <0.05 were considered statistically significant.

Analyses were performed with R version 3.5.1 (R Foundation for Statistical Computing, Vienna, Austria). Data were accessed through the Yale Open Data Access Platform (YODA project #2018-3813; Yale University, New Haven, CT, USA).

3. Results

3.1. Risk score and outcome

A total of 1088 patients were randomized in the COU-AA-302 trial and were included in the analysis. After a median follow-up in censored patients of 47.9 mo, the median OS was 33 mo (95% CI: 31–34.6), median rPFS was 12.2 mo (95% CI: 11–13.8), and median PSA PFS was 8.3 mo (95% CI: 8.3–8.3). Ninety-three (8.5%) patients on placebo were crossed over to abiraterone. Baseline characteristics, summarized in Table 1, were generally similar to those in PREVAIL. All variables included in the model except the treatment arm ($p = 0.07$) were significantly associated with OS in the multivariable Cox regression model (Supplementary Table 3).

The median prognostic index was 0.098 (interquartile range [IQR]: 0.063–0.176; Supplementary Fig. 2). The prognostic index was significantly associated with OS (HR: 2.83; 95% CI: 2.33–3.43; $p < 0.001$), rPFS (HR: 2.57;

Table 1 – Baseline characteristics

	COU-302 (N = 1088)	PREVAIL (N = 1709)	p value[a]
Albumin (g/dl)			–
Median (IQR)	4 (3.8–4.2)	3.9	
<4 g/dl	473 (43%)	NR	
Alk Phos (IU/l)			0.3
Median (IQR)	91 (69–136)	90	
≥ULN	310 (29%)	478 (28%)	
Hemoglobin (g/dl)			0.3
Median (IQR)	13.1 (12.2–13.8)	13.5	
≤12.5 g/dl	331 (30%)	502 (29%)	
LDH (IU/l)			0.15
Median (IQR)	185 (163–213.3)	185	
≥ULN	164 (15%)	293 (17%)	
PSA (ng/mL)			–
Median (IQR)	40 (15.8–108.4)	38.5	
>50 ng/mL	487 (45%)	NR	
NLR			0.6
Median (IQR)	2.62 (2–3.7)	2.65	
≥2.5	605 (56%)	944 (55%)	
Visceral metastases			<0.001
Yes	0	204 (12%)	
No. of bone mets			0.4
≥10 lesions	382 (35%)	556 (33%)	
Pain			0.3
Yes	371 (34%)	576 (34%)	
Months from Dx			–
Median	63.7 (33.6–104.4)	62.9	
<60 mo	521 (48%)	NR	
Treatment arm			0.5
Experimental arm	542 (50%)	870 (51%)	
Control arm	546 (50%)	839 (49%)	

Alk Phos = alkaline phosphatase; Dx = disease; IQR = interquartile range; NLR = neutrophil to lymphocyte ratio; LDH = lactate dehydrogenase; mets = metastases; NR = not reported in the original publication [13]; PSA = prostate-specific antigen; ULN = upper limit of normal.

[a] Distributions of dichotomized variables in the COU-AA-302 and PREVAIL trials were compared with tone-proportion Z tests, where data reported in the PREVAIL trial were used as the expected proportion.

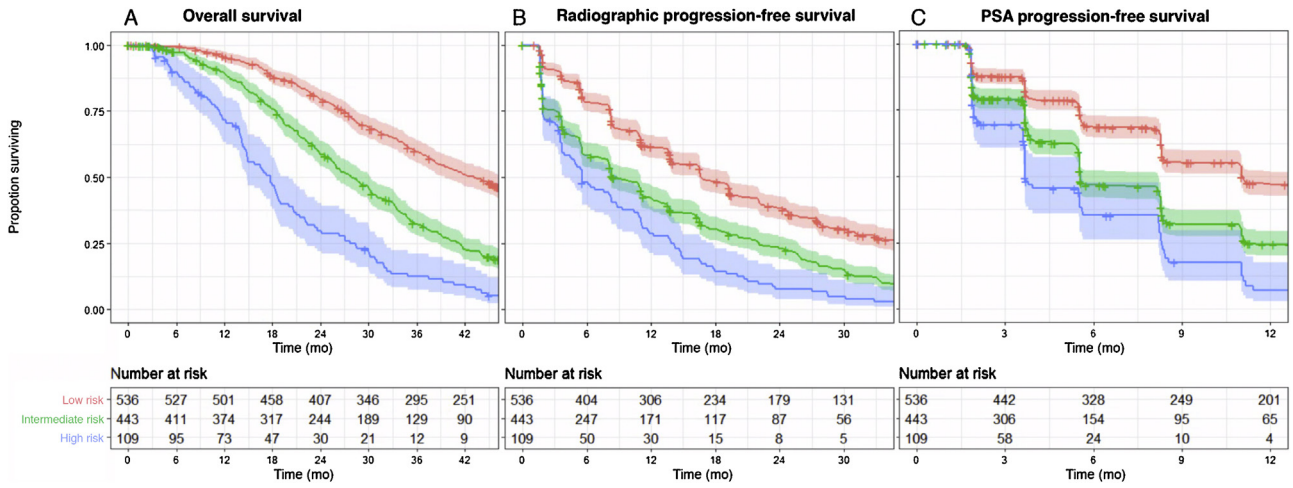

Fig. 1 – (A) Overall survival, (B) radiographic progression-free survival, and (C) PSA progression-free survival in low-, intermediate-, and high-risk groups.
PSA = prostate-specific antigen.

95% CI: 2.08–3.18; $p < 0.001$), and PSA PFS (HR: 2.25; 95% CI: 1.79–2.83; $p < 0.001$) as a continuous variable and also when categorized based on tertiles (Supplementary Fig. 3). The tAUC values for the OS, rPFS, and PSA-PFS models were 0.733, 0.667, and 0.662, respectively.

In total, 536 (49%) patients had low-risk, 443 (41%) patients had intermediate-risk, and 109 patients (10%) had high-risk disease according to the Armstrong risk group classification. The majority of patients exhibited two (16%), three (24%), or four (17%) risk factors (Supplementary Fig. 4). Of 756 patients who completed a discontinuation visit, radiographic progression was more frequent as a reason for treatment discontinuation in low-risk patients, while unequivocal clinical progression was more frequent in intermediate- or high-risk patients (Supplementary Table 4). A significant association between risk group and OS (HR: 2.15; 95% CI: 1.9–2.4; p value for linear trend <0.001), rPFS (HR: 2.15; 95% CI: 1.5–1.8; p value for linear trend <0.001), and PSA PFS (HR: 1.7; 95% CI: 1.5–1.9; p value for linear trend <0.001) was observed (Fig. 1). PSA and radiographic response rates were significantly higher in patients with low risk than in those with intermediate or high risk (Supplementary Table 5).

3.2. *Heterogeneity of treatment effect*

To evaluate the impact of treatment arm (abiraterone vs placebo) in each of the risk groups, we removed treatment arm as a cofactor in the risk group classification; 633 (58%), 386 (36%), and 69 (6.3%) patients were classified in the low-risk (three or fewer risk factors), intermediate-risk (four to six risk factors), and high-risk (seven to nine risk factors) groups. Of patients in the low-, intermediate-, and high-risk groups, 51%, 49%, and 48%, respectively, were treated with abiraterone. Among patients treated in the placebo arm, 72 (23%) patients in the low-risk, 20 (10%) patients in the intermediate-risk, and one (2.7%) patient in the high-risk groups were crossed over to receive abiraterone.

In the OS model, we observed a significant interaction between the treatment arm and the risk group ($p = 0.007$). The survival benefit associated with abiraterone was greater in low-risk (45.1 vs 37 mo; HR: 0.73; 95% CI: 0.59–0.89) than in intermediate-risk (25.8 vs 25.7 mo; HR: 0.96; 95% CI: 0.78–1.21) or high-risk (14.8 vs 16.9 mo; HR: 1.35; 95% CI: 0.8–2.28) patients (Fig. 2). Low-risk patients treated with abiraterone had a 2-yr OS benefit of 8% (82% vs 74%; $p = 0.009$) over placebo-treated patients, while this difference was of a nonstatistically significant 2.1% (55% vs 52%; $p = 0.5$) in intermediate-risk patients. High-risk patients treated with abiraterone had 3.1% lower 2-yr OS than placebo-treated patients (28% vs 31%; $p = 0.6$), although the difference was not statistically significant (Fig. 3).

A significant interaction between the treatment arm and the risk group ($p = 0.009$) was also observed when evaluating the rPFS model. Patients with low-risk disease derived a greater benefit from abiraterone treatment (21.3 vs 11 mo; HR: 0.56; 95% CI: 0.47–0.67) than those with intermediate-risk (11.1 vs 6.4 mo; HR: 0.80; 95% CI: 0.65–0.98) or high-risk (8.1 vs 4.9 mo; HR: 0.86; 95% CI: 0.53–1.4) disease (Table 2). Low-risk patients treated with abiraterone had a 24% 2-yr rPFS benefit (47% vs 23%) over placebo-treated patients. In intermediate-risk patients, this benefit was reduced to 4.9% (25% vs 20%; $p = 0.042$); no significant differences in 2-yr rPFS were observed in high-risk patients treated with abiraterone versus placebo (9.1% vs 6.1%; $p = 0.4$; Supplementary Fig. 5).

>We observed no significant interaction between the treatment arm and the risk group in the PSA-PFS model ($p = 0.44$). Abiraterone was associated with a similar PSA-PFS benefit in low-risk (13.8 vs 5.6 mo; HR: 0.58; 95% CI: 12–16.6), intermediate-risk (8.3 vs 4.6 mo; HR: 0.67; 95% CI: 8.3–8.5), and high-risk (5.5 vs 3.7 mo; HR: 0.55; 95% CI: 3.7–11) patients.

PSA response rates were higher in abiraterone-treated patients across all risk groups, with similar differences in

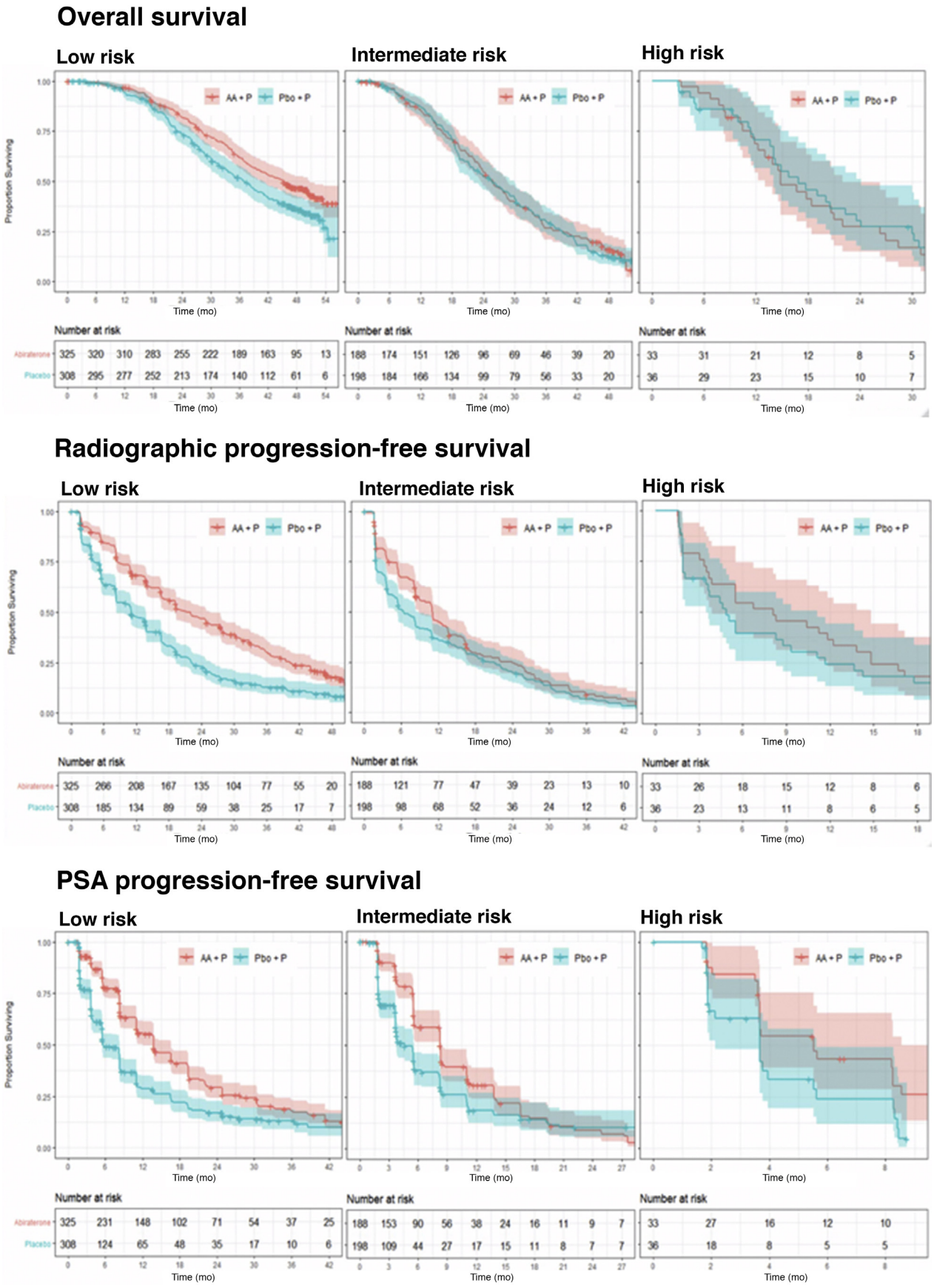

Fig. 2 – Impact of treatment arm on (A) overall survival, (B) radiographic progression-free survival, and (C) PSA progression-free survival in the in low- (left), intermediate- (center), and high-risk (right) groups.
PSA = prostate-specific antigen.

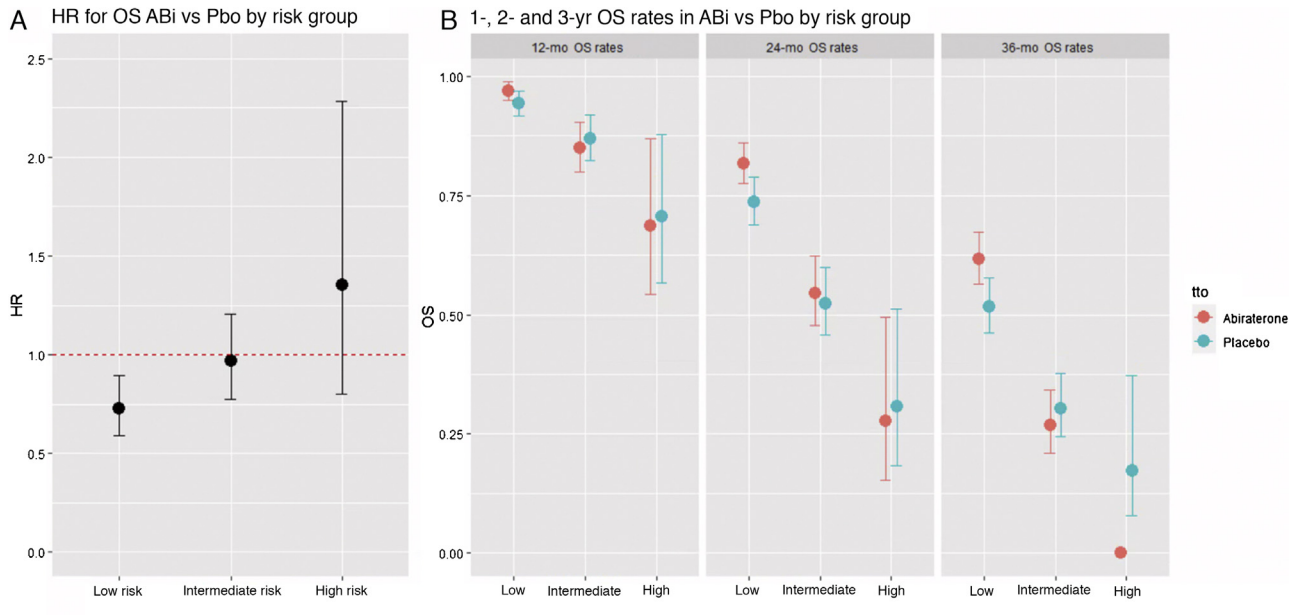

Fig. 3 – Impact of treatment arm on OS: (A) Cox regression hazard ratios and (B) survival rates in abiraterone- versus placebo-treated patients. Abi = abiraterone; HR = hazard ratio; OS = overall survival; Pbo = placebo.

Table 2 – Impact of treatment arm by risk group

	N	OS			rPFS			PSA PFS		
		Median (mo)	2-yr OS (%)	HR (95% CI)	Median (mo)	HR (95% CI)	2-yr rPFS (%)	Median (mo)	HR (95% CI)	2-yr PSA PFS (%)
Low risk (N = 633)										
Abiraterone	325	45.1	82	0.73 (0.59–0.89)	21.3	0.56	47	13.8	0.58	29
Placebo	308	37	74		11	(0.47–0.67)	23	5.6	(0.47–0.70)	17
Intermediate risk (N = 386)[a]										
Abiraterone	188	25.8	55	0.97	11.1	0.80	25	8.3	0.67	9
Placebo	198	25.7	52	(0.78–1.21)	6.4	(0.65–0.98)	20	4.6	(0.53–0.85)	10
High risk (N = 69)[a]										
Abiraterone	33	14.8	28	1.35	8.1	0.86	9.1	5.5	0.55	NA
Placebo	36	16.9	31	(0.8–2.28)	4.9	(0.53–1.4)	6.1	3.7	(0.31–0.99)	NA

CI = confidence interval; HR = hazard ratio; NA = not available; OS = overall survival; PFS = progression-free survival; PSA = prostate-specific antigen; rPFS = radiographic PFS.
[a] Risk group calculation was performed excluding the treatment arm.

low-risk (70% vs 36%; $p < 0.001$), intermediate-risk (62% vs 20%; $p < 0.001$), and high-risk (64% vs 25%; $p = 0.002$) groups. Similarly, radiographic response rates were higher in abiraterone-treated patients with low-risk (60% vs 24%; odds ratio [OR]: 4.8; $p < 0.001$) and intermediate-risk (38% vs 15%; OR: 3.4, $p = 0.002$). Differences in high-risk patients were not statistically significant (39% vs 31%; OR: 1.4; $p = 0.7$; Fig. 4).

3.3. *Risk score and quality of life*

We then assessed the relationship between baseline FACT-P scores and the risk classification. The median (IQR) baseline total FACT-P scores were 128 (IQR: 114–137) in low-risk, 124 (IQR: 110–134) in intermediate-risk, and 119 (IQR: 108–131) in high-risk patients ($p < 0.001$). Time to FACT-P deterioration was significantly associated with risk group (Supplementary Fig. 6). There was no significant interaction between the treatment arm and the risk group ($p = 0.7$); time to FACT-P progression was numerically longer in low-, intermediate-, and high-risk patients treated with abiraterone (Supplementary Fig. 7).

4. Discussion

Owing to the highly heterogeneous nature of advanced prostate cancer, the development of prognostic tools to assist in outcome prediction is of great importance, not only for the estimation of individual prognosis, but also for adequate stratification of patients in clinical trials. In view of the absence of validated predictive biomarkers for treatment selection, prognostic models can also assist in planning the timing for treatment initiation and, albeit

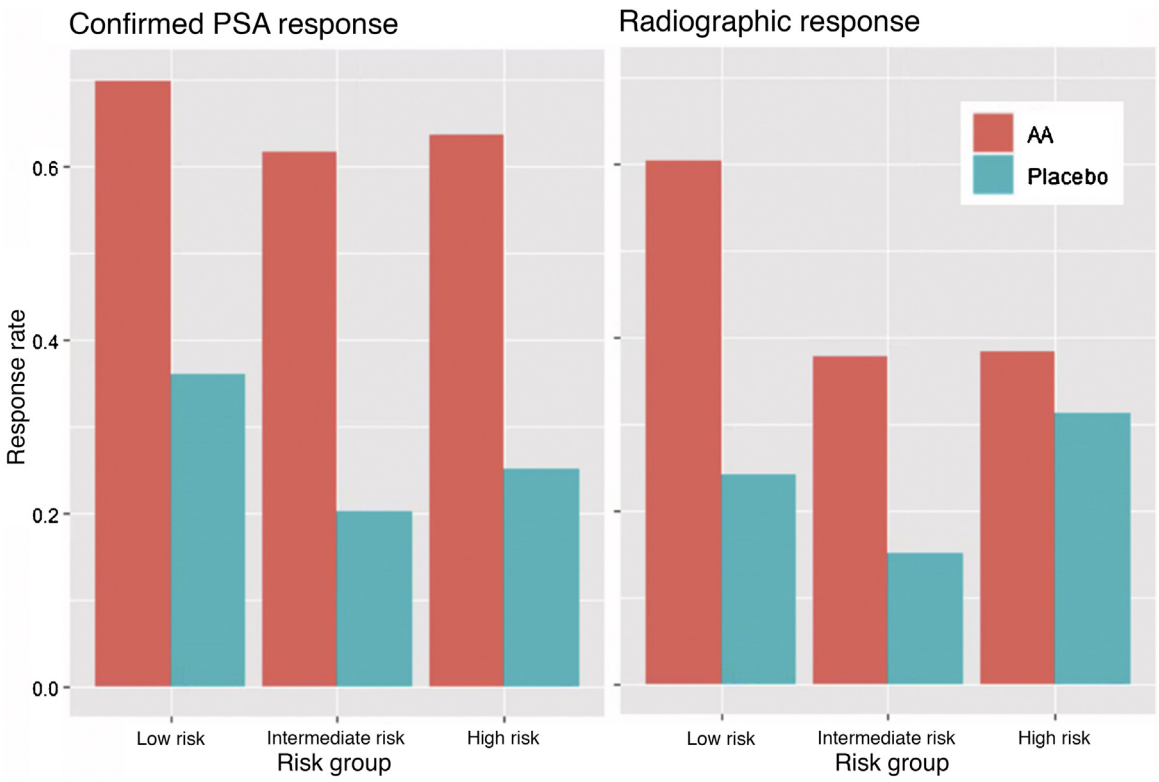

Fig. 4 – Impact of treatment arm on (A) PSA and (B) radiographic response rate by risk group.
AA = abiraterone; PSA = prostate-specific antigen.

indirectly, also in the selection of the treatment modality. Despite the number of prognostic models available, updated nomograms based on contemporary trial populations are needed to adequately assess prognosis in a shifting therapeutic landscape.

Our results support the external validity of the Armstrong prognostic model, confirming its prognostic value for asymptomatic or minimally symptomatic patients with mCRPC, with similar accuracy (tAUC: 0.732) to that presented in the initial derivation set from the PREVAIL trial (tAUC: 0.740) [13]. Trial populations were broadly comparable with that of the PREVAIL trial, with similar proportions of low-risk (49% vs 44%), intermediate-risk (41% vs 44%), and high-risk (10% vs 13%) patients, despite the fact that the presence of visceral disease was an exclusion in COU-AA-302 and not in PREVAIL.

Importantly, our analysis revealed a significant interaction for OS and rPFS between the risk group and the treatment arm affecting the magnitude of benefit from abiraterone, suggesting that a greater benefit from treatment occurs in the low-risk group. For instance, while abiraterone was associated with a 27% reduction of the risk of death and an 8% absolute benefit in 2-yr OS in low-risk patients, this benefit was limited to a 4% reduction of the risk of death and a 2.1% benefit in 2-yr survival in those with intermediate risk. Conclusions in high-risk patients were limited by the low number of patients in this subgroup.

We hypothesize that a more AR-driven biology in the low-risk subgroup, and thus a higher sensitivity to ARSIs, could be partially responsible for these differences. Differences in the proportion of placebo-arm patients receiving subsequent life-prolonging therapy between risk groups could also have impacted OS. Radiographic PFS, which is less influenced by subsequent therapy patterns, favored abiraterone over placebo in all subgroups, albeit the relative benefit was higher in low-risk patients (44% risk reduction) than in intermediate- or high-risk patients (20% and 15% risk reduction, respectively). Unfortunately, data on subsequent therapies were not available to address this hypothesis.

Our results suggest that classification using Armstrong risk groups can identify patients likely to experience a greater magnitude of benefit from novel hormonal therapies. If confirmed in datasets from similar populations, Armstrong risk groups should be included as a stratification factor in randomized clinical trials in order to account for a potential bias. Unfortunately, analyses from the PREVAIL study have not assessed the potential heterogeneity of treatment effect of enzalutamide in the different risk groups [13,14]. A different proportion of favorable- versus intermediate- or high-risk patients could have, for instance, contributed to the lack of survival benefit observed in first-line mCRPC patients with orteronel over placebo in the ELM-PC4 phase III clinical trial [17]; further analyses could

clarify this issue. Although the impact of the Armstrong risk group on benefit of patients treated with chemotherapy is unknown, cabazitaxel was recently shown to confer a higher clinical benefit rate than ARSIs in a randomized phase II study in mCRPC patients with adverse prognostic features [18]. If docetaxel is shown to retain activity in patients with intermediate- or high-risk disease, prospective evaluation of the predictive value of the Armstrong risk group classification in adequately powered randomized clinical trials comparing ARSIs versus taxanes would be warranted.

A number of limitations must be acknowledged. As previously mentioned, we could not evaluate the potential role of subsequent therapy in the interaction between the treatment arm and the risk group. Furthermore, results from pivotal phase 3 trials in metastatic hormone-sensitive prostate cancer (mHSPC) and nonmetastatic castration-resistant prostate cancer (nmCRPC) have shifted the standard of care from single androgen deprivation therapy (ADT) to ADT in combination with either docetaxel or androgen signaling inhibitors (abiraterone, enzalutamide, or apalutamide) in mHSPC or from ADT with/without vintage hormonal manipulations to ADT plus androgen signaling inhibitors (apalutamide, enzalutamide, or darolutamide) in nmCRPC. The fact that patients will now experience longer time to progression on the mHSPC or nmCRPC state, as well as the potential cross-resistance between agents makes it likely that this score will not predict survival adequately in pretreated patients. Finally, data on the molecular biology and levels of circulating tumor cells or circulating tumor DNA were lacking. These data are critical for an adequate assessment of the underlying biology of the disease and will need to be incorporated into future models.

5. Conclusions

In conclusion, we present evidence to support the validity of the Armstrong prognostic model for mCRPC treatment-naïve, minimally symptomatic patients. Additionally, we present evidence that abiraterone presents its greatest survival impact on patients with low-risk disease. Further research is needed to establish the predictive value of Armstrong risk groups in mCRPC. If confirmed, Armstrong risk groups could potentially be used for treatment selection in a scenario where the development of validated predictive biomarkers to guide therapy decisions represents an unmet clinical need.

Author contributions: David Lorente 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: Lorente, Olmos.
Acquisition of data: Lorente.
Analysis and interpretation of data: Lorente, Olmos.
Drafting of the manuscript: Lorente, Llacer, Lozano, de Velasco, Romero-Laorden, Castro, Olmos.
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Appendix A. Supplementary data

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