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ORIGINAL ARTICLE

The effect of chemotherapy on the exposure–response relation of abiraterone in metastatic castration-resistant prostate cancer

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Aims: To assess whether the exposure–response relation for abiraterone is different in pre-chemotherapy patients compared to post-chemotherapy patients with metastatic castration-resistant prostate cancer (mCRPC).

Methods: Data were collected from three clinical studies in mCRPC patients treated with abiraterone acetate. Cox regression analysis was used to determine the relation between abiraterone exposure and survival (progression-free survival [PFS] and overall survival [OS]). An interaction term was used to test whether chemotherapy pretreatment was an effect modifier. To investigate the effect of the previously defined exposure threshold of 8.4 ng/mL on survival, Kaplan–Meier analysis was used.

Results: In total, 98 mCRPC patients were included, of which 78 were pre-chemotherapy and 20 were post-chemotherapy patients. Chemotherapy pre-treatment in mCRPC setting appears to be an effect modifier. In pre-chemotherapy patients, no significant association between abiraterone exposure and survival was observed (HR 0.68 [95% CI 0.42–1.10], $P = .12$ and HR 0.85 [95% CI 0.46–1.60], $P = .61$, PFS and OS, respectively) and no longer survival was seen for patients with an abiraterone exposure above the predefined threshold. In contrast, a significant association was seen in post-chemotherapy patients (HR 0.30 [95% CI 0.12–0.74], $P = .01$ and HR 0.38 [95% CI 0.18–0.82] $P = .01$, PFS and OS, respectively), with an increased survival when exposed above this threshold.

Conclusion: Chemotherapy pretreatment in mCRPC setting modifies the abiraterone exposure–response relation. No relation between abiraterone exposure and survival was seen for pre-chemotherapy patients. Therefore, potentially lower doses can be used in this setting to prevent overtreatment and reduce financial toxicity.

The authors confirm that the Principal Investigator for this paper is Inge M. van Oort and that she had direct clinical responsibility for patients.

KEYWORDS
abiraterone acetate, castration-resistant prostate cancer, exposure–response, pharmacokinetics, survival

1 | INTRODUCTION

Abiraterone acetate (AA) in combination with prednisone has been shown to be an effective treatment in men with metastatic castration-resistant prostate cancer (mCRPC) and metastatic hormone-sensitive prostate cancer (mHSPC).[1–3] After administration, AA is rapidly hydrolysed to its active metabolite abiraterone. Abiraterone is a selective and irreversible inhibitor of CYP17, a key enzyme in the biosynthesis of androgens.[4] Large interpatient pharmacokinetic variability was shown for patients taking AA 1000 mg once daily, predominantly due to variation in absorption which is majorly affected by food intake.[5] Hence patients are instructed to take AA on an empty stomach. Therapeutic drug monitoring of abiraterone plasma levels has shown to be feasible, and there is accumulating evidence that targeting an optimal exposure may result in better treatment outcome.[6,7] It was demonstrated that patients with primary resistance to AA had a significantly lower abiraterone exposure compared to responders.[8] Furthermore, earlier studies in patients with mCRPC treated with AA showed that patients exposed to an abiraterone trough concentration (C_{min}) above 8.4 ng/mL had an improved progression-free survival (PFS) compared to patients below this threshold.[7,9] This exposure threshold was thereafter proposed for all mCRPC patients treated with AA. Over the past years, AA has been approved for the treatment of mCRPC patients pre- and post-chemotherapy and for patients with mHSPC.[1–3] However, it is unclear whether the earlier identified threshold is applicable for all these three different disease settings in which AA treatment is given. Genomic alterations, including copy number changes or mutation in oncogenes or tumour suppressor genes such as *TP53*, *RB1* or *PTEN*, have higher prevelance in mCRPC patients compared to localised or de novo metastatic prostate cancer patients.[10] Androgen receptor (*AR*) alterations (e.g., amplifications, structural variants and mutations) are associated with castration-resistance and inferior responses to AA.[10–12] In addition, *TP53* alterations are also associated with resistance to taxanes and inferior outcome to AA.[13,14] These aberrations accumulate following progression to androgen deprivation and docetaxel.[15] Hence, patients with less advanced disease, or fewer therapeutic regimens, might be more sensitive for AA.

In earlier studies that defined the abiraterone exposure threshold, no distinction was made between mCRPC patients pre- or post-chemotherapy, while PFS is markedly different in both groups. In first-line mCRPC patients AA increased radiological PFS (rPFS) from 8.3 to 16.5 months, whereas in docetaxel-pretreated mCRPC patients AA increased rPFS from 3.6 to 5.6 months compared to placebo + prednisone.[1,2] Possibly, the threshold that should be aimed for in both disease settings might be distinctly different. We therefore aimed to assess whether the exposure–respone relation for abiraterone is different for pre-chemotherapy patients compared to post-chemotherapy patients with mCRPC.

What is already known about this subject

- Patients with an abiraterone exposure (trough concentration) > 8.4 ng/mL showed favourable progression-free survival (PFS).
- For defining this threshold, no distinction was made between patients who received abiraterone before or after chemotherapy in mCRPC setting, while PFS on abiraterone treatment is markedly different for both groups of patients.

What this study adds

- Chemotherapy pretreatment in mCRPC setting alters the exposure–response relation of abiraterone in mCRPC patients.
- Patients without docetaxel pretreatment in mCRPC setting seem to be more sensitive for abiraterone compared to docetaxel-pretreated patients.
- Potentially lower doses of abiraterone can be used in chemotherapy-naïve patients to prevent overtreatment and reduce financial toxicity.

2 | METHODS

2.1 | Study design

Pharmacokinetic (PK) and survival data were collected from three clinical studies performed in the Netherlands (ANDROPS, OPTIMUM NCT02426333 and SNACK NCT02883166). In these clinical studies patients with mCRPC starting AA therapy were included (study details are summarised in the Supporting Information). All studies were conducted in accordance with Good Clinical Practice and the Declaration of Helsinki and approved by the medical ethics committee "Commissie Mensgebonden Onderzoek Regio Arnhem Nijmegen". Written informed consent was obtained from all patients before entering the study.

2.2 | Pharmacokinetic assessments

Blood samples were drawn for PK assessment of abiraterone at several time points in each study (PK sampling details are listed in the Supporting Information). Abiraterone plasma levels were measured using a validated liquid chromatography tandem mass spectrometry

method.[16] The assay ranges from 1 to 500 ng/mL.[16] Precision, expressed as coefficient of variation values, and accuracy, expressed as deviations from the nominal concentrations, were below 13.4% and within 95–102%, respectively.[16] Details of this analytical method are described by Benoist et al.[16] For the PK analysis non-linear mixed-effects modelling was used, with the software package NONMEM V7.4 using the first order conditional estimation method with interaction (FOCE-I). As a starting point for the analysis, the previously developed population PK model for abiraterone by Stuyckens et al. was used.[17] The PK parameters of the model were re-estimated based on the PK samples collected in the three clinical studies (PK modelling details are shown in the Supporting Information, Table S1, Figures S1 and S2). The model-derived empirical Bayes estimates for trough concentrations (C_{min}) exactly 24 hour after AA intake were used as input for the PK analysis. The predictive performance of using a random sample to predict trough concentrations was assessed (details of the method and results can be found in the Supporting Information and Figure S5).

2.3 | Statistics

The association between the individual averaged log-normalised abiraterone C_{min} and PFS (biochemical, radiographic or clinical progression) and overall survival (OS) was assessed by univariable Cox regression. The influence of docetaxel treatment in mCRPC setting on the abiraterone exposure–response relation, was determined by comparing docetaxel-pretreated patients in mCRPC setting, with mCRPC patients who were not treated with docetaxel in mCRPC setting. Patients that received six or fewer cycles of docetaxel in the hormone-sensitive prostate cancer setting, according to the CHAARTED or STAMPEDE studies, were classified as pre-chemotherapy patients. Francini et al. investigated that in a cohort of 102 patients of which 50 had received androgen deprivation therapy (ADT) alone, and 52 had ADT + docetaxel (according to CHAARTED/STAMPEDE), the efficacy of abiraterone or enzalutamide treatment is similar regardless of previous use of upfront docetaxel.[18] We have confirmed this observation on our dataset by Kaplan–Meier analysis and log-rank test (results are shown in the Supporting Information and Figure S3).

First, it was tested whether chemotherapy pretreatment in mCRPC setting was a confounder for the exposure–response relation by multivariable Cox regression. Second, an interaction term was incorporated to test if previous chemotherapy was an effect modifier. If effect modification was present ($P < .05$), separate effect estimates for abiraterone exposure on PFS and OS were determined for pre- and post-chemotherapy mCRPC patients by multivariable Cox regression. The independent variables incorpatered in the multivariable Cox regression models were individual averaged log-normalised abiraterone C_{min} levels and chemotherapy pretreatment (pre-chemotherapy *vs* post-chemotherapy). To correct for other clinical parameters that impact survival, the following covariables were added to the model based on previous published prognostic models: PSA > 39.5 ng/mL, LDH > ULN, ALP > ULN and albumin < LLN.[19,20] Additionally, to investigate the effect of the previously defined exposure threshold of 8.4 ng/mL on PFS and OS, Kaplan–Meier analysis with log-rank test was used. The effect of the exposure threshold was also tested for patients treated according to CHAARTED or STAMPEDE studies to confirm that these patients can be classified as pre-chemotherapy (results are shown in the Supporting Information and Figure S4).

Finally, to determine whether abiraterone C_{min} levels were different between pre- and post-chemotherapy patients, an independent *t*-test on log-transformed data was performed. Statistical significance was set at $P < .05$. All statistical analyses were performed using R version 3.6.2 with R-studio version 1.1.463 as an interface and the R package survival version 3.7-2 (https://CRAN.R-project.org/package=survival).

2.4 | Nomenclature of targets and ligands

Key protein targets and ligands in this article are hyperlinked to corresponding entries in http://www.guidetopharmacology.org, and are permanently archived in the Concise Guide to PHARMACOLOGY 2019/20.[21]

3 | RESULTS

3.1 | Patients

In total, 107 patients with 636 PK samples were included (Figure 1). Four patients were excluded from the analysis because they stopped AA treatment before PK sample collection. Three patients were included in more than one of the discussed studies. Four abiraterone levels were excluded from the dataset, because they were above the higher limit of quantification. A total of 103 patients with 632 PK samples were included in the population PK model development.

For the exposure–response analysis, three patients were excluded due to AA toxicity before the first response evaluation (< 12 weeks). Two patients were excluded because they received AA in hormone-sensitive prostate cancer setting. For patients of the SNACK study, plasma levels of the experimental dosage (500 mg AA OD with a continental breakfast) were excluded, because bioequivalence was not established.[22] Finally, 98 mCRPC patients with 487 PK samples were included in the exposure–response analysis. A total of 78 (80%) were mCRPC patients who received AA pre-chemotherapy and 20 (20%) were mCRPC patients who received AA post-chemotherapy. Baseline characteristics are summarised in Table 1. Detailed results of the study population (dosing information and exposure distribution) of the three studies individually are provided in the Supporting Information.

The median follow-up time was 539 days (range 64–2587 days). At time of analysis, 73 (74%) patients had progressed and 43 patients (44%) died. Among the pre-chemotherapy mCRPC patients, 55 (71%) patients showed progression with a median PFS of 470 days and

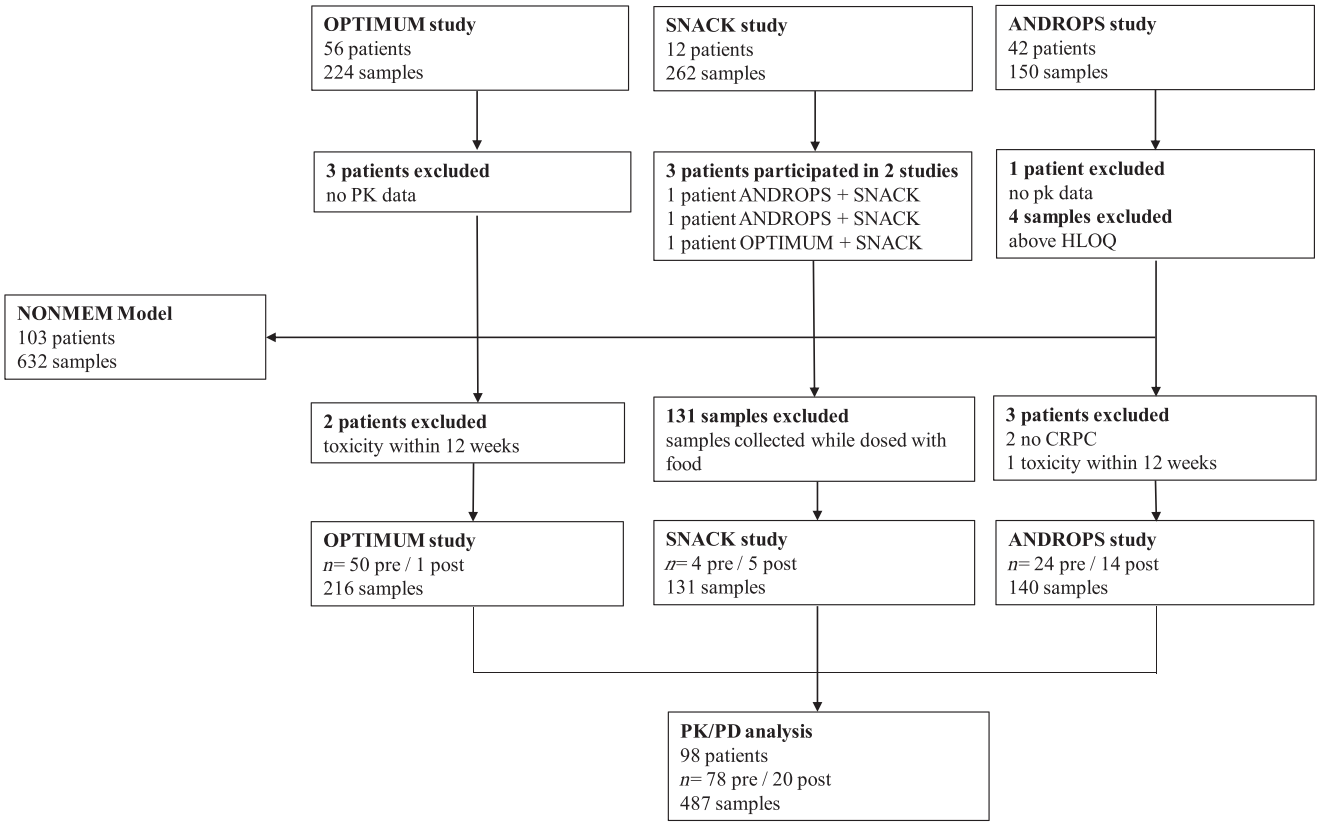

FIGURE 1 Flowchart of inclusion

27 (35%) died with a median OS of 1067 days. Among the post-chemotherapy mCRPC patients, 18 patients (90%) showed progression with a median PFS of 187 days and 16 patients (80%) died with a median OS of 405 days.

3.2 | Exposure–response analysis

In the total group of patients a trend towards a beneficial effect of higher abiraterone exposure on PFS and OS was seen, although not significant (hazard-ratio (HR) 0.72 [95% confidence interval (CI) 0.50–1.05]; $P = .086$ and HR 0.79 [95% CI 0.51–1.25]; $P = .317$, respectively). Previous chemotherapy in mCRPC setting was not a confounder but was shown to modify the effect of abiraterone exposure on PFS and OS (interaction term $P = .047$ and $P = .013$, respectively).

Therefore, the relation between abiraterone exposure and treatment outcome should be analysed separately for both groups of patients. In patients treated with AA pre-chemotherapy in mCRPC setting, no effect of abiraterone exposure on PFS and OS was seen after correcting for other clinical parameters that affect treatment outcome (i.e. PSA > 39.5 ng/mL, LDH > ULN, ALP > ULN and albumin < LLN) (HR 0.68 [95% CI 0.42–1.10], $P = .12$ and HR 0.85 [95% CI 0.46–1.60], $P = .61$). Whereas in the post-chemotherapy mCRPC patients higher abiraterone exposure was significantly associated with longer PFS and OS also after correcting for the clinical parameters (HR 0.30 [95% CI 0.12–0.74], $P = .01$ and HR 0.38 [95% CI 0.18–0.82], $P = .01$).

Furthermore, we analysed the effect of the previously defined threshold of 8.4 ng/mL on PFS and OS. In the group of pre-chemotherapy mCRPC patients 17% ($n = 13$) had an exposure below the threshold, compared to 40% ($n = 8$) of post-chemotherapy mCRPC patients. In the pre-chemotherapy mCRPC patients an exposure below the threshold was not associated with shorter survival (median PFS and OS below *vs* above the threshold: 546 *vs* 462 days; $P = .81$ and 1370 *vs* 1067 days; $P = .58$, respectively, Figure 2). While in post-chemotherapy mCRPC patients a trend towards shorter PFS and a significantly shorter OS was seen for patients with abiraterone exposure below *vs* above the threshold (median PFS 148 *vs* 268 days; $P = .15$; and median OS 361 *vs* 553 days; $P = .041$; Figure 3). Finally, it was shown that pre-chemotherapy mCRPC patients were exposed to significantly higher abiraterone C_{min} levels compared to post-chemotherapy mCRPC patients (geometric mean C_{min} 13.5 ng/mL *vs* 9.7 ng/mL, $P = .048$).

4 | DISCUSSION

In this study we observed a different exposure–reponse relation of abiraterone for pre- and post-chemotherapy mCRPC patients. To our knowledge, this is the first study revealing that chemotherapy

TABLE 1 Baseline characteristics

	Overall ($n = 98$)	Pre-chemotherapy ($n = 78$)	Post-chemotherapy ($n = 2$
Age at baseline (years)	70 (65–76)	71 (65–78)	68 (63–70)
BMI (kg/m^2)	27 (25–30)	27 (25–30)	26 (25–28)
PSA (ng/mL)	54 (24–159)	47 (23–145)	63 (45–238)
PSA doubling time (months)	3.0 (2.1–4.7)	3.6 (2.2–5.8)	2.7 (1.6–2.9)
LDH (U/L)	221 (195–260)	220 (195–256)	228 (195–276)
ALP (U/L)	96 (72–141)	86 (69–127)	125 (104–189)
Bilirubin (ng/mL)	6 (5–11)	7 (4–11)	7 (4–11)
Albumin (g/dL)	39 (35–42)	40 (36–43)	35 (34–39)
C_{min} < 8.4 ng/mL	21 (21)	13 (17)	8 (40)
eGFR < 60 mL/min	18 (18)	15 (19)	3 (15)
ALAT > 45 IU/L	8 (8)	8 (10)	0 (0)
ASAT > 35 IU/L	20 (20)	14 (18)	6 (30)
ECOG performance status			
0	45 (46)	41 (53)	4 (20)
1	23 (24)	18 (23)	5 (25)
2	3 (3)	2 (3)	1 (5)
Gleason score at diagnosis			
≤ 7	26 (27)	21 (27)	5 (25)
≥ 8	64 (65)	51 (65)	13 (65)
No. previous lines of therapy			
0	70 (71)	70 (90)	0 (0)
1	18 (18)	8 (10)	10 (50)
2	7 (7)	0 (0)	7 (35)
≥ 3	3 (3)	0 (0)	3 (15)
Previous systemic treatment[a]			
Docetaxel	20	0	20
Enzalutamide	9	1	8
Cabazitaxel	2	0	2
Other	12	7	5
Previous docetaxel in hormone-sensitive prostate cancer setting[b]	18	18	0

Data are presented as median (Q1–Q3) for continuous data or *n* (%) for categorical data.
BMI, body mass index; PSA, prostate-specific antigen; LDH, lactate dehydrogenase; ALP, alkaline phosphatase; eGFR, estimated glomerular filtration rate; ALAT, Alanine aminotransferase; ASAT, aspartate aminotransferase; ECOG, Eastern Cooperative Oncology Group.
[a]In castration resistant prostate cancer setting.
[b]According to CHAARTED/STAMPEDE trial.

pretreatment in mCRPC setting modifies the abiraterone exposure–response relation. This finding confirms our hypothesis that the threshold for abiraterone exposure might be different for pre- and post-chemotherapy mCRPC patients. Furthermore, we observed a significantly lower abiraterone exposure in post-chemotherapy *vs* pre-chemotherapy patients.

Previous work identified an efficacy exposure threshold for abiraterone of 8.4 ng/mL in 61 mCRPC patients, which was confirmed in another 62 mCRPC patients.[7,9] However, neither study differentiated on chemotherapy pretreatment. In our relatively large group of mCRPC patients who received AA before chemotherapy in mCRPC setting ($n = 78$), we could not confirm this threshold and no significant exposure–response relation was observed. Patients with a lower abiraterone exposure showed a similar response compared to patients with a higher abiraterone exposure. This might suggest that pre-chemotherapy mCPRC patients could be treated with lower doses of AA while maintaining effectiveness. These findings are in line with Szmulewitz et al. who showed that 250 mg AA once daily taken with a low-fat breakfast is noninferior to standard dosing, while a significantly lower exposure was observed (approximately 2 ng/mL) which is far below the earlier defined efficacy threshold.[23] The majority of the included patients (>80%) in Szmulewitz et al. were

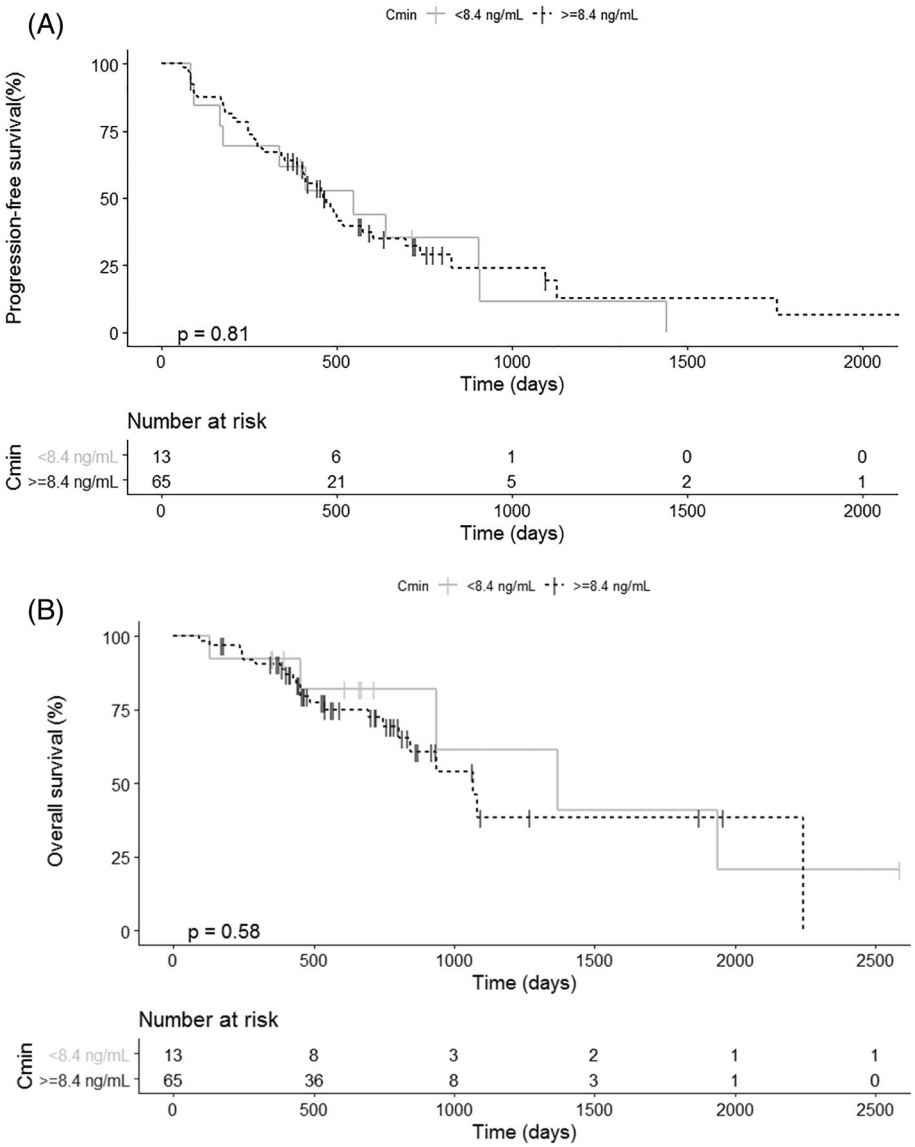

FIGURE 2 Kaplan–Meier plots for progression-free survival (A) and overall survival (B) in pre-chemotherapy metastatic castration-resistant prostate cancer (mCRPC) patients with a mean abiraterone C_{min} above (black dotted line) or below (grey line) the threshold of 8.4 ng/mL

pre-chemotherapy mCRPC patients. Therefore, it might well be that mCRPC patients who are treated with AA pre-chemotherapy require a much lower dose for optimal efficacy which could reduce financial toxicity. Since treatment with AA is moving up in line towards hormone-sensitive prostate cancer, it is worthwhile to explore the optimal abiraterone exposure in different disease settings. Based on our findings, the defined threshold of 8.4 ng/mL seems not to be applicable in early stages of disease (mHSPC and pre-chemotherapy mCRPC) and general use might cause overtreatment.

Chemotherapy-preteated mCRPC patients with a higher abiraterone exposure showed longer survival compared to patients with a lower abiraterone exposure. This suggests that these patients might be less sensitive to abiraterone treatment compared to pre-chemotherapy patients. This hypothesis is supported by Xu et al., who found a higher effective concentration for abiraterone in chemotherapy-pretreated patients compared to pre-chemotherapy mCRPC patients, indicating lower sensitivity of tumour cells in chemotherapy-pretreated patients.[24] *TP53*, *RB1*, *PI3K* and *AR* are a few of the alterations that are associated with acquisition of castration resistance and following chemotherapy resistance.[11–14] Additionally, pretreatment can lead to *AR* (enhancer) alterations (e.g., amplifications, structural variants and mutations), which has been associated with a worse response to AA.[11,25,26] Additional translational studies will have to identify the post-chemotherapy genomic landscape that may be associated with the AA exposure–response relation. Potentially, a higher exposure can overcome this resistance mechanism.

The previously established exposure threshold of 8.4 ng/mL might be applicable for post-chemotherapy patients. Possibly in some patients, dose increments or intake with food is necessary to achieve this exposure. Therefore, therapeutic drug monitoring (TDM) could play an important role in this setting to optimise treatment outcomes.

Friedlander et al. investigated whether a dose increment of 1000 mg AA twice daily at the time of resistance would increase

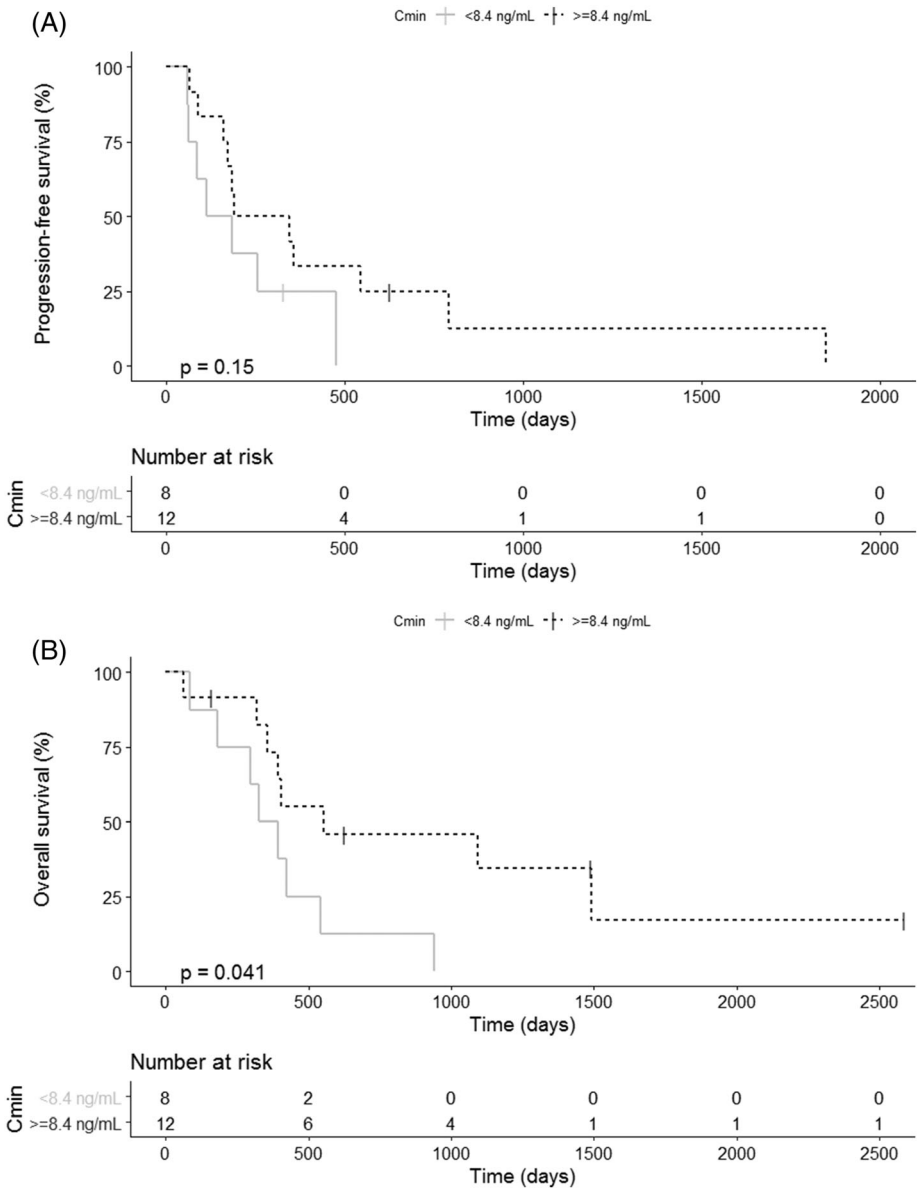

FIGURE 3 Kaplan–Meier plots for progression-free survival (A) and overall survival (B) in post-chemotherapy metastatic castration-resistant prostate cancer (mCRPC) patients with a mean abiraterone C_{min} above (black dotted line) or below (grey line) the threshold of 8.4 ng/mL

clinical effects.[8] Although the dose increment was safe, it showed limited clinical utility. However, the effect of higher AA exposure at the start of treatment in chemotherapy-pretreated mCRPC patients was not investigated. Further research is needed to investigate if a higher starting dose of AA or concomitant food intake can increase survival in post-chemotherapy mCRPC patients. Our developed population-pharmacokinetic model could be implemented in the clinic for the purpose of model-informed precision dosing.

A significantly lower exposure was observed for chemotherapy-pretreated patients compared to pre-chemotherapy patients. While in registration studies no effect of previous chemotherapy on abiraterone exposure was observed, a similar trend towards higher exposure in less pretreated patients was found in other real-world studies.[5,6,9,17] A possible explanation might be the uncontrolled setting of AA intake in real-world studies and the risk of noncompliance. Although patients are instructed to take AA before breakfast, differences in abiraterone exposure can even be observed depending on the time of breakfast after AA intake.[27,28] Furthermore, it was shown that the extent of the food effect on abiraterone absorption is dependent on health status.[17] Post-chemotherapy mCRPC patients have an overall worse health status which could affect food intake, and therefore the influence of food on the absorption might be less pronounced. However, information regarding patients' diet (e.g., amount of fat and time of food intake) is missing. Additionally, the influence of other comorbidities on the absorption of AA is unknown. Further research is required to explain these yet unclarified differences in exposure.

A limitation of our study is the relatively small group of chemotherapy-pretreated patients consisting of only 20 patients that were included in the observational cohort study. As this is the first study identifying a different exposure–response relation in patients pretreated with chemotherapy *vs* patients without chemotherapy pretreatment in mCRPC setting, our findings add to the existing data so far. Additionally, our group of pre-chemotherapy patients is relatively

large ($n = 78$). Previous studies investigating the exposure–response relation did not differentiate on chemotherapy pretreatment. The exposure threshold was investigated in Carton et al. in only 61 mCRPC patients in which 21% of the patients were docetaxel pretreated.[7] However, it is not known whether these patients all had a lower abiraterone exposure. Van Nuland et al. confirmed the exposure threshold in a real-life cohort of 62 mCRPC patients, in which 42% of the patients were chemotherapy-pretreated. Suprisingly, in the group of patients with an exposure below the threshold, 65% were chemotherapy-pretreated *vs* 25% in the group of patients with an exposure above the threshold.[9] So it might well be possible that if both studies analysed the patients who received AA before or after chemotherapy in mCRPC setting independently, results would be consistent with our findings. Since the survival benefit of AA is much shorter in chemotherapy-pretreated patients, this might influence their original results.

Our findings indicate that in different disease settings (e.g., mHSPC, mCRPC pre- and post-chemotherapy) different exposure thresholds should be aimed for to optimise AA treatment outcome. For pre-chemotherapy patients we have shown that a lower exposure did not lead to a shorter survival (PFS or OS). Therefore we suggest that in the early disease setting (mHSPC and pre-chemotherapy mCRPC), patients might be more sensitive for abiraterone and potentially lower dosages (e.g. 250–500 mg) can be used in this setting. Applying lower doses in these settings will have an immense impact on the financial toxicity of the treatment of patients with prostate cancer. Further research is needed to confirm that lower dosages in early disease setting are noninferior to standard dosing.

5 | CONCLUSION

In our study we identified a different exposure–response relation in patients who received AA before or after chemotherapy in the mCRPC setting. Patients without docetaxel pretreatment in the mCRPC setting seem to be more sensitive for abiraterone compared to docetaxel-pretreated patients. However, these results need to be confirmed in a larger group of patients. No relation between abiraterone exposure and survival (PFS or OS) was seen for patients receiving abiraterone before chemotherapy in the mCRPC setting. Therefore, potentially lower doses can be used in this setting to prevent overtreatment and reduce financial toxicity.

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COMPETING INTERESTS

N.P.E.: received research grants from Astellas, Janssen-Cilag and received honoraria from Sanofi and Bayer. N.M.: Advisory role (compensated and institutional): Roche, MSD, BMS, Bayer, Astellas and Janssen. Research support (institutional): Astellas, Janssen, Pfizer, Roche and Sanofi Genzyme. Travel support: Astellas, MSD. I.M. v.O.: received research grants from Astellas, Janssen, and Bayer, and has a consulting/advisory role for Astellas, Janssen, Bayer, Roche, and Mdx health. All remaining authors have declared no conflicts of interest.

CONTRIBUTORS

E.B. and J.O. wrote the manuscript; G.B., N.P.E., N.M. and I.O. designed the research; E.B., G.B., J.O., N.M., I.O., R.H. and N.P.E. performed the research; E.B., J.O., R.D. and R.H. analysed the data.

DATA AVAILABILITY STATEMENT

All data generated and/or analysed during the current study are available from the corresponding author on reasonable request.

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SUPPORTING INFORMATION

Additional supporting information may be found in the online version of the article at the publisher's website.

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