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Prostate Cancer

## Third-line Life-prolonging Drug Treatment in a Real-world Metastatic Castration-resistant Prostate Cancer Population: Results from the Dutch Castration-resistant Prostate Cancer Registry

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### Abstract

**Background:** Evidence concerning third-line life-prolonging drugs (LPDs) in the treatment of metastatic castration-resistant prostate cancer (mCRPC) patients is incomplete.

**Objective:** To evaluate third-line LPD outcomes in a real-world cohort of mCRPC patients, identify variables associated with overall survival (OS), and establish a prognostic model.

**Design, setting, and participants:** Patients with mCRPC who were progressive on second-line LPD before July 1, 2017 were retrospectively identified from the Dutch Castration-resistant Prostate Cancer Registry (CAPRI) and followed until December 31, 2017.

**Outcome measurements and statistical analysis:** Association of potential risk factors with OS was tested by Cox proportional hazard models after multiple imputation of missing baseline characteristics. A predictive score was computed from the regression coefficient and used to classify patients into risk groups.

**Results and limitations:** Of 1011 mCRPC patients progressive on second-line LPD, 602 (60%) received third-line LPD. Patients receiving third-line LPD had a more favorable prognostic profile at baseline and longer median OS than patients with best supportive

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care (10.4 vs 2.4 mo,  $p < 0.001$ ). Eastern Cooperative Oncology Group performance status 1 and  $\geq 2$  (hazard ratio [HR] 1.51,  $p < 0.007$  and HR 3.08,  $p < 0.001$ , respectively), opioid use (HR 1.55,  $p = 0.019$ ), visceral metastases (HR 2.09,  $p < 0.001$ ), hemoglobin  $< 7$  mmol/l (HR 1.44,  $p < 0.002$ ), prostate-specific antigen  $\geq 130$   $\mu\text{g/l}$  (HR 1.48,  $p = 0.001$ ), alkaline phosphatase  $\geq 170$  U/l (HR 1.52,  $p < 0.001$ ), and lactate dehydrogenase  $\geq 250$  U/l (HR 1.44;  $p = 0.015$ ) were associated with shorter survival. Harrell's C-index was 0.74. The median OS values for low-, low-intermediate-, high-intermediate-, and high-risk groups were 14, 7.7, 4.7, and 1.8 mo, respectively. Limitations include the retrospective design.

**Conclusions:** We developed a prognostic model and identified a subgroup of patients in whom third-line LPD treatment has no meaningful benefit. Our results need to be confirmed by prospective clinical trials.

**Patient summary:** We reported outcomes from third-line life-prolonging drugs in metastatic prostate cancer patients and developed a prognostic model that could be used to guide treatment decisions.

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## 1. Introduction

Prostate cancer is the most common cancer among men in the Western world [1]. Part of these patients will eventually progress and develop metastatic castration-resistant prostate cancer (mCRPC) [2]. In 2004, docetaxel, a member of the taxane drug class, was the first treatment to improve overall survival (OS) of mCRPC patients [3]. In the past years, several new therapeutic agents, including cabazitaxel, abiraterone acetate, enzalutamide, and radium-223, have also been registered for the treatment of mCRPC based on a survival benefit. The outcomes of these life-prolonging drugs (LPDs) as first- and/or second-line (post-docetaxel) treatment have been well established [4–9].

It is common practice to use these drugs as a third-line LPD treatment, after first- and second-line LPD treatment, in the hope to obtain a cumulative benefit [10]. To date, randomized controlled trials of third-line LPDs in mCRPC patients are scarce [11]. The reports on third-line LPDs are particularly retrospective and based on small cohorts of patients receiving one specific third-line LPD [12–16]. Patients with mCRPC who are on third-line LPD may have worse outcomes, compared with those on first- and second-line LPD treatment, due to more advanced stages in general, decreased performance status, worse tolerance to treatments [17], and possible cross-resistance [18].

Thus, third-line LPDs might not be appropriate for all patients. Selection of patients with mCRPC who will benefit from third-line LPD treatment is crucial to improve outcomes, reduce unnecessary toxicity, improve quality of life (QoL), and reduce costs [19]. Prediction of treatment outcome may allow for better patient selection. Nevertheless, current prognostic models for survival using clinical and laboratory baseline variables in mCRPC patients have been described only in first- or second-line LPDs [20–23].

The aim of this retrospective study was to evaluate outcomes of third-line LPD treatment in a real-world cohort of mCRPC patients, to identify clinical and laboratory variables associated with survival, and to finally assess the impact of these variables in a risk score.

## 2. Patients and methods

### 2.1. Study design and setting

Castration-resistant Prostate Cancer Registry (CAPRI) is an investigator-initiated, observational, multicenter cohort study in 20 hospitals in The Netherlands. The study design has been previously described [24]. Patients with mCRPC were included retrospectively from January 1, 2010 until December 31, 2015. Metastatic CRPC was defined either by the criteria set by the European Association of Urology [25] or by the treating physician. The study is registered in the Dutch Trial Registry as NL3440 (NTR3591).

### 2.2. Objectives

The aim of this study is to investigate the outcomes of third-line LPD treatment in a real-world population of mCRPC patients, identify clinical and laboratory variables related to survival outcomes, and assess the impact of these variables in a risk score.

### 2.3. Participants

Metastatic CRPC patients with progressive disease on or after a second-line LPD, before July 1, 2017, were included in the analysis. All patients had received two lines of LPD treatment, of which at least one of the two previous lines was docetaxel. They were categorized into two groups: patients receiving a third-line LPD and patients receiving best supportive care (BSC).

Patients previously treated with docetaxel for hormone-sensitive metastatic prostate cancer ( $n = 14$ ) were excluded from the analysis.

### 2.4. Follow-up and data collection

Predefined and readily available data from medical records were retrospectively collected by trained data managers. Baseline characteristics were included in the analysis if they

were documented 3 wk prior to 3 wk after the progression date after a second-line LPD. All patients were followed until death, loss to follow-up, or December 31, 2017. Follow-up duration was calculated as the time from the date of progression on a second-line LPD to the last recorded date.

### 2.5. Outcomes

Outcomes were OS, treatment duration (TD), and prostate-specific antigen (PSA) response. OS was calculated in months from the date of progression after second-line LPD treatment to the date of death from any cause. Patients alive at the end of the study or lost to follow-up were censored at the last recorded date.

TD was defined as the interval between the start and stop of third-line LPD treatment. If the stop date was unknown, TD was specified as the time from the start of third-line LPD to the start of next treatment, or as the time from the start of third-line LPD to the end of follow-up if third-line treatment was the last treatment. Patients on treatment at the end of follow-up were censored at the last recorded date.

PSA response was defined as the maximum change from baseline PSA levels (in percentages) without confirmation of a second measure. In case no decline was present, responses were measured at 12 wk (according to Prostate Cancer Clinical Trials Working Group 3 criteria for response measurement [26]) or if treatment was <12 wk, at the end of treatment or start of next treatment. PSA response was defined as a  $\geq 50\%$  PSA decline from baseline.

### 2.6. Statistical analysis

Descriptive statistics were performed. The *t* test (or Mann–Whitney *U* test for nonparametric variables) was used for continuous variables and the Pearson chi-square was used for categorical variables. OS and TD were estimated using the Kaplan–Meier method and were compared between groups using the log-rank test. A waterfall plot was made to indicate PSA response. Missing baseline characteristics were imputed using multiple imputation with Monte Carlo Markov Chain method. Selection of prognostic factors was based on clinical applicability (routinely collected and used by clinicians), previous research, and expert opinion [27]. Continuous variables were categorized using the median cutoff or clinically applicable cutoffs. Multivariable Cox proportional hazard analysis using a backward stepwise procedure was performed on pooled data for OS. A simplified prediction rule was obtained by rounding the regression coefficients to half points, which were multiplied by two for easier clinical applicability. A risk score for the prediction of OS was then calculated for each patient. Patients could be categorized into different risk groups based on the survival curves of each risk score. The prognostic performance of the prediction model was evaluated using Harrell's concordance index (C-index) in the original dataset. A *p* value of  $\leq 0.05$  was considered statistically significant. Statistical analyses were performed using IBM SPSS Statistics, version 22.0 (SPSS Inc., Chicago, IL, USA).

## 3. Results

At the end of the study, 3616 CRPC patients were included in 20 hospitals. A total of 1011 mCRPC patients (28%) had progression on or after a second LPD treatment and were included in the analysis. At database cutoff, 826 deaths (82%) had occurred, 127 patients (13%) were lost to follow-up, and 58 patients (6%) were still alive.

All patients were previously treated with docetaxel and with abiraterone acetate ( $n = 525$ , 52%), enzalutamide ( $n = 282$ , 28%), cabazitaxel ( $n = 155$ , 15%), docetaxel rechallenge ( $n = 31$ , 3.0%) or radium-223 ( $n = 18$ , 2.0%).

Of these 1011 mCRPC patients, 602 (60%) received a third-line LPD. The third-line LPD consisted of cabazitaxel ( $n = 213$ , 35%), abiraterone acetate ( $n = 137$ , 23%), enzalutamide ( $n = 129$ , 21%), radium-223 ( $n = 78$ , 13%), and docetaxel ( $n = 45$ , 8.0%). An overview of previous treatment lines and third-line treatment is provided in Supplementary Table 1.

### 3.1. Baseline characteristics

Baseline characteristics of mCRPC patients at the progression date of a second-line LPD, according to the subsequent third-line LPD or not, are shown in Table 1. Patients receiving a third-line LPD had a more favorable prognostic profile (significantly younger, better Eastern Cooperative Oncology Group performance status [ECOG PS], less opioid use, less visceral metastases, higher hemoglobin [Hb], lower alkaline phosphatase [ALP], and lower lactate dehydrogenase [LDH]) compared with patients who received BSC.

### 3.2. OS and risk-scoring system

The median OS (mOS) from progression on a second-line LPD was 6.5 mo (95% confidence interval [CI] 5.9–7.2). The mOS was longer for patients receiving a third-line LPD (10.4 mo, 95% CI 9.2–11.6) compared with patients who received BSC (2.4 mo, 95% CI 2.1–2.7; Fig. 1).

Univariable analysis revealed baseline ECOG PS, opioid use, symptoms, visceral metastases, lymph node metastases, Hb, PSA, ALP, LDH, and period from castration to CRPC as being significant variables for the prediction of survival in mCRPC patients progressing on a second-line LPD (Table 2).

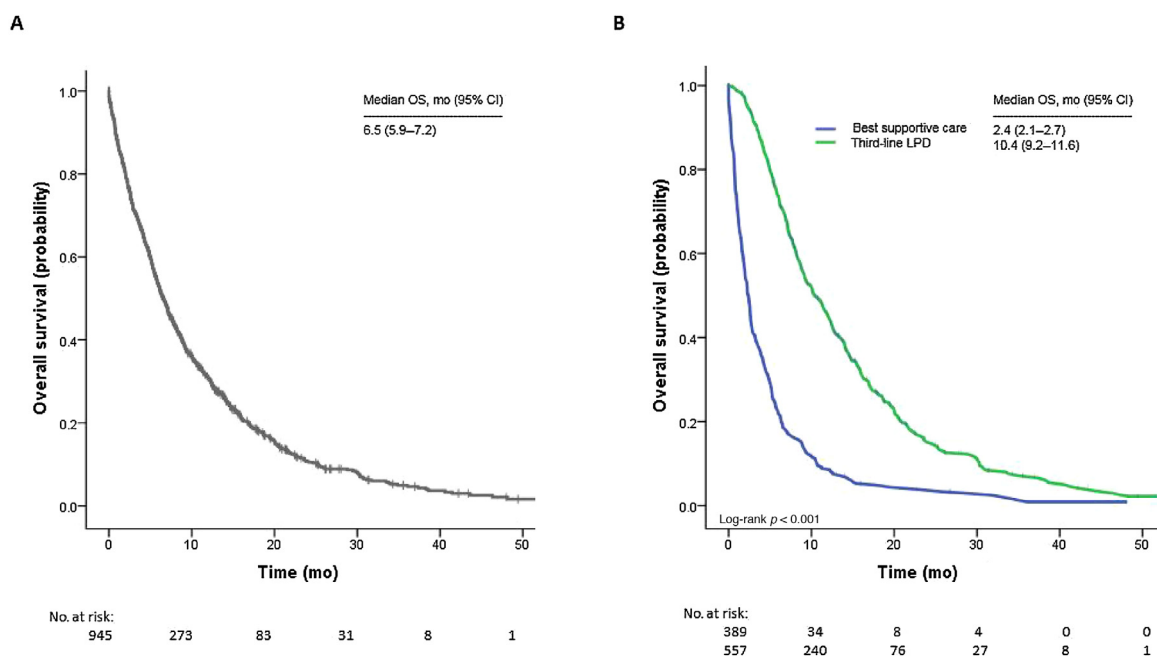
The multivariable Cox regression analysis of pooled data identified seven variables independently associated with OS: ECOG PS of 1 and  $\geq 2$  (HR 1.51, 95% CI 1.13–2.00,  $p = 0.007$  and HR 3.08, 95% CI 2.31–4.10,  $p < 0.001$ , respectively), opioid use (HR 1.55, 95% CI 1.10–2.19,  $p = 0.019$ ), visceral metastases (HR 2.09, 95% CI 1.76–2.49,  $p < 0.001$ ), Hb  $< 7.0$  mmol/l (HR 1.44, 95% CI 1.15–1.84,  $p = 0.002$ ), PSA  $\geq 130$   $\mu\text{g/l}$  (HR 1.48, 95% CI 1.20–1.82,  $p = 0.001$ ), ALP  $\geq 170$  U/l (HR 1.52, 95% CI 1.26–1.84,  $p < 0.001$ ), and LDH  $> 250$  U/l (HR 1.44, 95% CI 1.09–1.90,  $p = 0.015$ ); these were related to worse survival and included in the final model. The Harrell's C-index was 0.74.

Based on their regression coefficients, we assigned a score of 1 point to ECOG PS of 1, opioid use, Hb  $< 7.0$  mmol/l, PSA  $\geq 130$   $\mu\text{g/l}$ , ALP  $\geq 170$  U/l, and LDH  $> 250$  U/l. A score of 2 points was assigned to ECOG PS  $\geq 2$  and

**Table 1 – Baseline characteristics at the time of progression after a second-line LPD in mCRPC patients according to receiving a third-line LPD or best supportive care.**

Characteristics	Total group of patients progressive after a second-line LPD (n = 1011)	Missing	Best supportive care (n = 409)	Missing	Third-line LPD (n = 602)	Missing	p value
Age (yr)	71.6 ± 7.5	21 (2.1)	73.0 ± 7.8	0	71.0 ± 7.3	21 (3.5)	0.032
ECOG PS		508 (50)		229 (56)		279 (46)	<0.001
0	93 (9)		15 (4)		78 (13)		
1	280 (28)		67 (16)		213 (35)		
≥2	130 (13)		98 (24)		32 (5)		
Opioid use	219 (22)	605 (60)	127 (31)	225 (55)	92 (12)	380 (63)	<0.001
Symptomatic	704 (70)	81 (8)	346 (85)	13 (3)	358 (60)	68 (11)	<0.001
Metastatic site							
Bone	871 (86)	96 (10)	355 (87)	41 (10)	516 (86)	55 (9)	0.139
Visceral	169 (17)	493 (49)	91 (22)	202 (49)	78 (13)	291 (48)	<0.001
Lymph nodes	469 (46)	382 (38)	195 (48)	163 (40)	274 (46)	219 (36)	0.030
Hemoglobin (mmol/l)	7.1 ± 1.2	303 (30)	6.8 ± 1.2	111 (27)	7.4 ± 1.1	192 (32)	<0.001
Platelets (10 <sup>9</sup> /l)	250 (193–315)	314 (31)	238 (167–322)	117 (29)	256 (205–313)	197 (33)	0.032
Prostate-specific antigen (µg/l)	133 (42–413)	126 (13)	174 (42–491)	64 (16)	118 (42–358)	62 (10)	0.058
Alkaline phosphatase (U/l)	170 (99–353)	182 (18)	260 (128–506)	72 (18)	139 (88–253)	110 (18)	<0.001
Lactate dehydrogenase (U/l)	289 (213–420)	411 (41)	389 (241–730)	154 (38)	251 (203–360)	257 (43)	<0.001

ECOG PS = Eastern Cooperative Oncology Group performance status; LPD = life-prolonging drug; mCRPC = metastatic castration-resistant prostate cancer; SD = standard deviation.  
Data are presented as mean ± SD, median (interquartile range), or n (%).

**Fig. 1 – Kaplan-Meier curves and at-risk tables for overall survival (OS) from progression after a second-line LPD (A) for the total group (n = 1011), (B) classified by third-line LPD (n = 602) or best supportive care (n = 409). The p values were obtained from log-rank tests for the homogeneity of Kaplan-Meier curves between third-line LPD and best supportive care.**

CI = confidence interval; LPD = life-prolonging drug; OS = overall survival.

presence of visceral metastases (Supplementary Table 2A). Taking into account the survival curves of the calculated risk scores, patients could be categorized into different risk groups: low-risk (score 0), low-intermediate risk (score 1–3), high-intermediate risk (score 4–6), and high-risk (score 7–9; Supplementary Table 2B). The low-risk group included

103 patients (10%), the low-intermediate-risk group included 467 patients (46%), the high-intermediate-risk group included 341 patients (34%), and the high-risk group included 56 patients (6%). Median survival times for these low-, low-intermediate-, high-intermediate-, and high-risk groups were 14.0 mo (95% CI 10.7–17.3), 7.7 mo (95% CI 6.6–8.9),

**Table 2 – Univariable and multivariable analyses of different prognostic variables for overall survival in patients with mCRPC progression after a second-line LPD.**

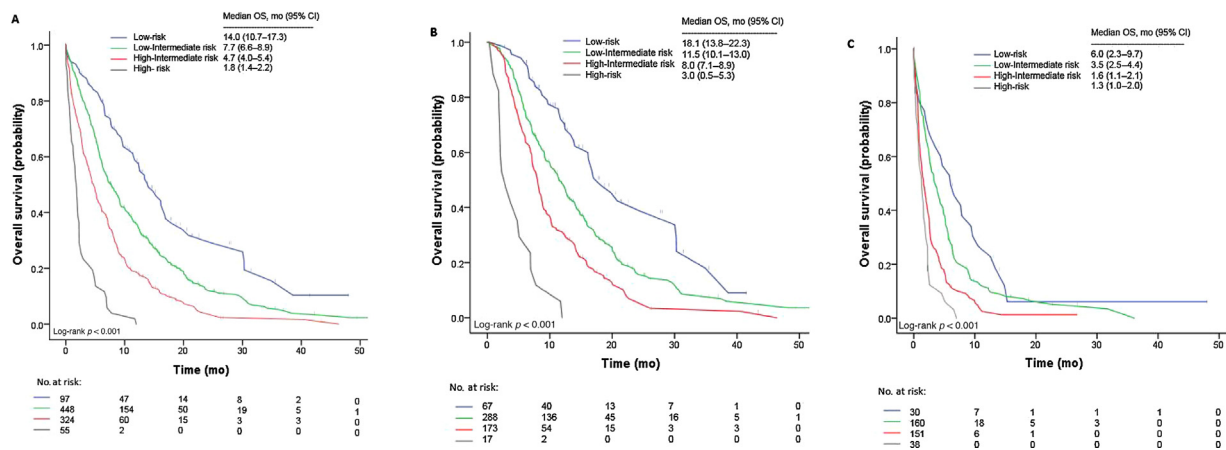
Variable	n	Event	Censored	Missing	Univariable analysis <sup>a</sup>		Multivariable analysis <sup>a,b</sup>				
					Hazard ratio (95% CI)	p value	Hazard ratio (95% CI)	p value	β <sup>c</sup>	Points	
ECOG PS	503	420	83	508		<0.001					
0	93				1		1		0		
1	280				1.74 (1.33–2.29)		1.51 (1.13–2.00)	0.007	0.409	1	
≥2	130				4.55 (3.35–6.18)		3.08 (2.31–4.10)	<0.001	1.123	2	
Opioid use	406	350	56	605		<0.001			0.019		
No	187				1		1		0		
Yes	219				2.18 (1.75–2.73)		1.55 (1.10–2.19)		0.438	1	
Symptomatic	925	754	171	86		<0.001					
No	224				1		1		0		
Yes	701				2.07 (1.73–2.47)						
Visceral metastases	511	409	102	500		<0.001			<0.001		
No	344				1		1		0		
Yes	167				2.13 (1.73–2.62)		2.09 (1.76–2.49)		0.738	2	
Lymph node metastases	622	508	114	389		0.002					
No	158				1		1		0		
Yes	464				1.38 (1.12–1.69)						
Hemoglobin (mmol/l)	708	594	114	303		<0.001			0.002		
<7	307				1		1		0		
≥7	401				2.22 (1.88–2.62)		1.44 (1.15–1.84)		0.372	1	
Platelets (10 <sup>9</sup> /l)	697	584	113	314		0.535					
<250	344				1		1		0		
≥250	353				1.05 (0.89–1.24)						
Prostate-specific antigen (μg/l)	885	723	162	126		<0.001			0.001		
<130	441				1		1		0		
≥130	444				1.73 (1.49–2.00)		1.48 (1.20–1.82)		0.393	1	
Alkaline phosphatase (U/l)	833	682	151	178		<0.001			<0.001		
<170	415				1		1		0		
≥170	418				2.23 (1.91–2.60)		1.52 (1.26–1.84)		0.421	1	
Lactate dehydrogenase (U/l)	600	505	95	411		<0.001			0.015		
<ULN	236				1		1		0		
≥ULN	364				2.24 (1.86–2.69)		1.44 (1.09–1.90)		0.365	1	
Time from castration to CRPC (mo)	988	806	182	23		0.012					
<12	475				1		1		0		
≥12	513				1.19 (1.04–1.37)						

B = beta regression coefficient; CI = confidence interval; CRPC = castration-resistant prostate cancer; ECOG PS = Eastern Cooperative Oncology Group performance status; LPD = life-prolonging drug; mCRPC = metastatic castration-resistant prostate cancer; n = number of patients; ULN = upper limit of normal.

<sup>a</sup> Cox regression model.

<sup>b</sup> The final sample used in the multivariate analysis consisted of 1011 patients; 826 patients died and 185 were censored.

<sup>c</sup> The coefficient of each variable was rounded to half point and then multiplied by a constant (2) for easier clinically applicability.



**Fig. 2 – Kaplan-Meier curves and risk tables for overall survival (OS) from progression after a second-line LPD according to the four risk groups for (A) the total group (n = 1011), (B) patients receiving a third-line LPD (n = 602), and (C) patients receiving best supportive care (n = 409). CI = confidence interval; LPD = life-prolonging drug; OS = overall survival.**

4.7 mo (95% CI 4.0–5.4), and 1.8 mo (95% CI 1.4–2.2), respectively ( $p < 0.001$ ; Fig. 2A).

A third-line LPD was started in 69% patients (71 out of 103) in the low-risk group, 64% patients (299 out of 467) in the low-intermediate-risk group, 53% patients (181 out of 341) in the high-intermediate-risk group, and 30% patients (17 out of 56) in the high-risk group. The mOS for these risk groups, according to whether or not treated with a third-line LPD, are depicted in Fig. 2.

A nomogram, integrating the significant independent variables for OS, is provided in Supplementary Figure 1.

### 3.3. TD and PSA response of third-line LPD treatment

At the end of follow-up, 26 patients (4.3%) with a third-line LPD were still on treatment. The median TD (mTD) for a third-line LPD was 3.3 mo (95% CI 3.0–3.5). PSA decline on the third-line LPD was assessable in 560 (93%) patients and observed in 130 (22%) patients.

The mTD for the four risk groups (low-, low-intermediate-, high-intermediate-, and high-risk groups) were 4.6 mo (95% CI 3.8–5.4), 3.4 mo (95% CI 3.2–3.6), 2.7 mo (95% CI 2.4–3.0), and 1.4 mo (95% CI 1.1–1.7), respectively ( $p < 0.001$ ; Fig. 3). PSA response rates (>50% PSA response) were 24% (18/76 patients), 22% (66/301 patients), 23% (41/181 patients), and 6% (one/17 patients), respectively. Waterfall plot of the PSA responses are shown in Fig. 4.

## 4. Discussion

To our knowledge, this is the first large multicenter real-world cohort, evaluating the outcomes of mCRPC patients

progressing on a second-line LPD, treated according to the views and opinions of their treating physicians.

We observed the mOS of 6.5 mo from progression of second-line LPD. The mOS was longer in patients with a third-line LPD than in patients receiving BSC (10.4 vs 2.4 mo), but TD was short (3.3 mo) and PSA response was low (22%). Our results confirm the potential cumulative survival benefit (mOS 7.1–15.8) of previous retrospective studies on third-line LPD treatment [13–15].

Pivotal phase 3 trials on first- and second-line LPD treatment in mCRPC patients reported the mOS of 14.0–34.7 mo. The difference in OS can partially be explained by the fact that patients treated in trials notably differ from patients who receive standard treatment options only [24] and the more advanced disease state of patients after two systemic treatment lines. This is reflected by poor performance score, high disease burden, and high ALP, LDH, and PSA. As mCRPC progresses, disease control becomes more difficult [28]. Possible cross-resistance with previous treatments can further decrease treatment effect [18]. Moreover, tolerability to new systemic treatments can be worse [17], leading to early discontinuation.

Evidence concerning optimal sequencing of third-line LPDs is limited, but suggests that patients may not respond to androgen receptor-targeted therapies (ARTs; abiraterone or enzalutamide) in third line after progression on prior ARTs due to cross-resistance [10,17,29]. This is recently prospectively confirmed by a study of de Wit et al. [11], which reported increased mOS in patients receiving cabazitaxel compared with those receiving an ART (13.6 vs 11.0 mo) after prior docetaxel and the other ART. Since all patients had progression on an alternative ART within 12 mo, they were not comparable with our study

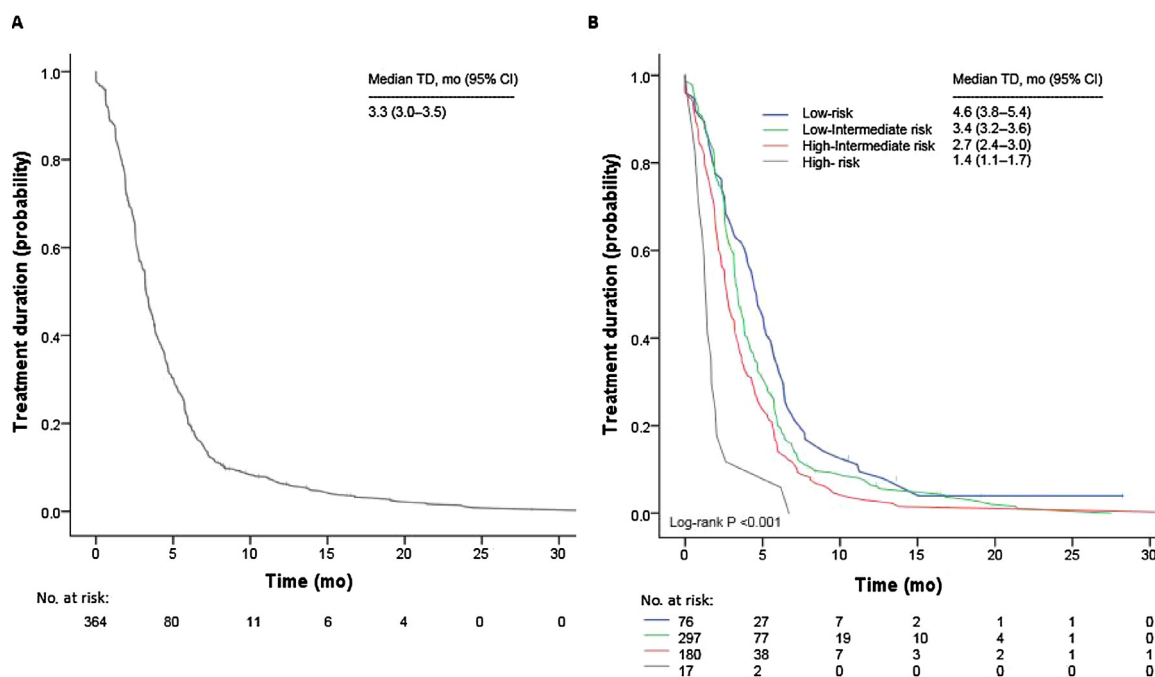


Fig. 3 – Kaplan-Meier curves and at-risk tables for the treatment duration of a third-line LPD (A) for all patients receiving a third-line LPD ( $n = 602$ ) and (B) according to the four risk groups. CI = confidence interval; LPD = life-prolonging drug; TD = treatment duration.

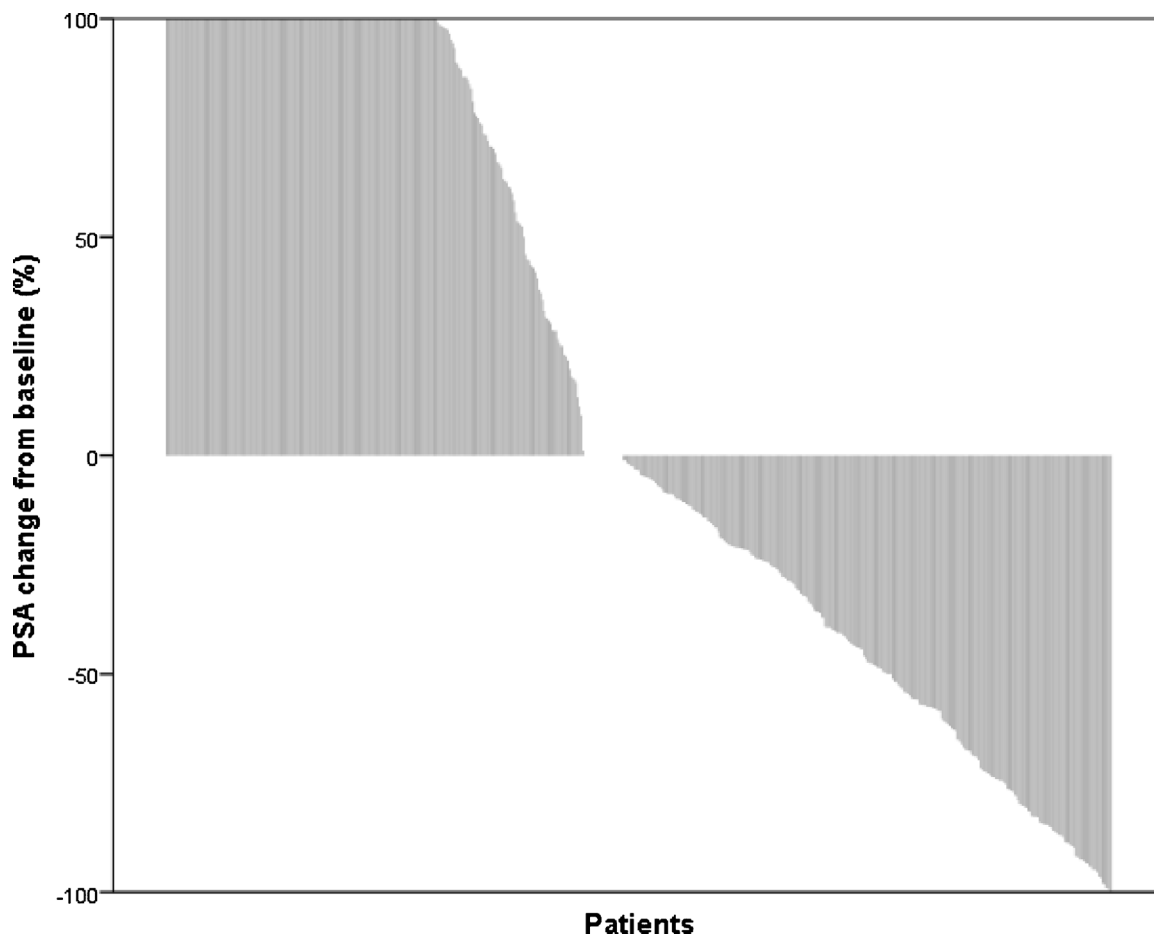


Fig. 4 – Waterfall plots of maximum PSA changes from baseline for patients treated with a third-line LPD ( $n = 602$ ). LPD = life-prolonging drug; PSA = prostate-specific antigen.

population. Our analysis identified seven independent prognostic variables associated with survival, namely ECOG PS, opioid use, visceral metastases, Hb, PSA, ALP, and LDH. These variables were able to distinct four risk groups (low-, low-intermediate-, high-intermediate-, and high-risk) for patients who had progressive disease after a second-line LPD, with corresponding median survival times of 14.0, 7.7, 4.7, and 1.8 mo, respectively ( $p < 0.001$ ).

Especially, high-risk patients had remarkably short mOS. Moreover, high-risk patients treated with a third-line LPD had worse mOS than patients receiving BSC in low- or low-intermediate-risk groups. These results suggest that high-risk patients may derive no meaningful benefit from third-line LPDs in clinical practice, which is supported by the short mTD and low PSA responses. Therefore, high-risk patients should not be treated with third-line LPDs; instead, they should be treated with BSC.

Our prognostic model allows for the stratification of four risk groups with widely differing mOS. It is important for physicians to consider these different survival times in medical decision making. Proper patient selection for third-line LPD treatment is crucial to improve outcomes, reduce unnecessary toxicity, and improve QoL. Also, careful

consideration is warranted considering possible low cost effectiveness.

This study is not without limitations. First, our results are limited by the absence of previously identified risk factors such as albumin level [27]. However, albumin is not a routinely assessed parameter in real-world clinical practice. Moreover, many patients had missing values of one or more baseline variables at progression on second-line LPD due to the retrospective nature of the study. Imputation of missing baseline data offers a valid solution for multivariable analysis [30]. Second, the effect of third-line LPD in other outcomes such as QoL and cost effectiveness could not be included in this analysis. Lastly, the identified prognostic model has not yet been externally validated and is therefore not yet suitable for clinical use.

Nevertheless, our prognostic model was developed using a large number of patients with mCRPC who were progressive after second-line LPD, and the number of deaths in the pooled analysis was substantial, providing good statistical power. Furthermore, this prognostic model is based on readily available clinical and laboratory variables, and risk groups can be calculated easily. Although our prognostic model is based on retrospective data, it was able to identify



four risk groups with differing survival times, suggesting that the identified variables may assist in the selection of patients for third-line LPD treatment in daily clinical practice and thereby improving efficacy of these potentially toxic and expensive LPD.

## 5. Conclusions

Third-line LPDs might not be appropriate for all mCRPC patients, which is supported by the short mTD and low PSA responses observed in our study. We developed a simple prognostic model, based on routinely used clinical and laboratory parameters, and identified a high-risk subgroup in whom no meaningful benefit from third-line LPD is derived in clinical practice. Our results need to be confirmed by further prospective trials.

**Author contributions:** Jessica C.L. Notohardjo 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:* Notohardjo, Kuppen, Westgeest, van den Eertwegh, Uyl-de Groot, Gerritsen.

*Acquisition of data:* Kuppen, Westgeest.

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*Obtaining funding:* Westgeest, Uyl-de Groot, Gerritsen.

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## Appendix A. Supplementary data

Supplementary material related to this article can be found, in the online version, at doi:<https://doi.org/10.1016/j.euf.2020.03.009>.

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